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SUPERIOR EXTENSION OF INTRAOPERATIVE BRAIN DAMAGE IN CASE OF NORMOTHERMIC SYSTEMIC PERFUSION DURING CORONARY ARTERY BYPASS OPERATIONS

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Objective: **Despite the controversies on the potential detrimental effects of normothermic cardiopulmonary bypass on neurologic outcome, to date no correlation between the severity of intraoperative brain lesions and the cardiopulmonary bypass temperature used at operation has been reported. This study compares the prevalence and the severity of brain lesions in patients who underwent operation in condition of normothermic versus hypothermic systemic perfusion.** ***Methods:*** **Data are derived from the analysis of 2987 consecutive primary isolated myocardial revascularizations performed at our institution between April 1990 and January 1997. Of these cases, 1385 procedures were hypothermic and 1602 procedures were normothermic systemic perfusion. In all cases the neurologic outcome and extent of ischemic areas were prospectively recorded.** ***Results:*** **Overall, 31 patients had a perioperative stroke (1.0%). The prevalence of neurologic events was similar in the 2 groups (15 cases in the hypothermic group and 16 cases in the normothermic perfusion group; *P*, not significant). However, the mean Glasgow Outcome Scale score and computed tomography-demonstrated extent of brain lesions were significantly worse in the normothermic group.** ***Conclusions:*** **Although the prevalence of intraoperative stroke was similar with hypothermic or normothermic cardiopulmonary bypass, the use of normothermic systemic perfusion was associated with more extended brain damage at computed tomographic scan and with a worse neurologic outcome. These results demand caution in the use of normothermic cardiopulmonary bypass and claim further investigation on the neurologic safety of normothermia. (J Thorac Cardiovasc Surg 1999;118:432-7)**

Although the prevalence of neurologic events in patients undergoing hypothermic versus normothermic cardiopulmonary bypass (CPB) has been the subject of several investigations,[1-4] the extent and the severity of perioperative brain damage have never been examined with regards to the CPB temperature used at operation.

Since April 1990, in an attempt to reduce the prevalence of neurologic complications in patients submitted to coronary artery operation, our institution adopted a neurologic risk stratification of patients undergoing primary isolated coronary artery bypass grafting (CABG) based on a protocol of systematic screening of the ascending aorta and internal carotid arteries. This protocol, which has already been described in detail,[5] included the careful clinical and tomographic assessment of brain damage in those patients who experienced perioperative neurologic complications and the prospective introduction of all data in a computerized database.

From the beginning of the study, no major modifications in the surgical and anesthesiologic technique were adopted, with the exception of a change in the CPB temperature and myocardial protection introduced in October 1993 (when we switched from hypothermic to normothermic CPB).

This shift from hypothermic to normothermic systemic perfusion, combined with a careful prospective

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evaluation of the brain lesion in patients who experienced a perioperative stroke, gave us the opportunity to evaluate in the present study the influence of the temperature of extracorporeal circulation on the prevalence and, most of all, the severity of the neurologic damage.

Patients and methods

Neurologic risk assessment. All patients undergoing primary isolated elective or emergency CABG procedures at our institution since April 1990 were submitted to a preoperative evaluation of the neurologic risk that included (1) echo Doppler evaluation of the internal carotid arteries and (2) preoperative and intraoperative assessment of the ascending aorta (by careful evaluation of preoperative chest radiography and aortography, intraoperative digital palpation, and ultrasonography). The detailed modalities of these examinations and the classification of their results have already been described elsewhere.[5]

On the basis of this screening, the patients were divided into 3 categories of neurologic risk (in case of concomitant aortic and carotid disease of different severity, the classification was based on the most severe lesion): (1) patients at low risk: patients without lesions and with slight internal carotid artery disease or slight disease of the ascending aorta; (2) patients at moderate risk: patients with moderate internal carotid artery stenosis and/or moderate atherosclerosis of the ascending aorta; and (3) patients at high risk: patients with severe internal carotid artery stenosis and/or markedly atherosclerotic ascending aorta.

Evaluation of perioperative neurologic complications. Perioperative neurologic complications were classified according to the definitions given in the Appendix; patients with transient ischemic attacks were not considered in the data analysis.

In all patients, a neurologic evaluation was performed by a cardiovascular anesthesiologist at the moment of the patient awakening from anesthesia.

In cases of neurologic abnormalities, a complete neurologic examination was performed by a consultant neurologist immediately after the onset of symptoms, 24 hours later, at regular intervals of 1 or more days (depending on the clinical status) and at discharge.

In case of stroke, the neurologic outcome was assessed with the Glasgow Outcome Scale (GOS).[6] A GOS score was assigned concomitantly with the neurologic evaluations by a neurologist and a cardiovascular anesthesiologist; disagreements were resolved by consensus after a common reevaluation.

In patients with the clinical evidence of neurologic complications of any type, brain computed tomographic (CT) scans were performed immediately after the onset of symptoms, 24 to 48 hours later, after any change in the neurologic status, and the day before discharge.

All scans were prospectively performed and independently evaluated by 2 expert neuroradiologists; disagreements were resolved by common re-examination.

Table I. *Main preoperative and intraoperative characteristics of patients of the 2 groups*

Variable	*Hypothermic group*	*Normothermic group*	P *value*
Cases (n)	1385	1602	—
Mean age (y)	59.8 ± 3.9	59.6 ± 4.1	.17
M/F (n)	4.3/1	4.5/1	.45
Risk factors (n)			
Diabetes	248	299	.62
Smoking	885	972	.07
Dislipidemia	1211	911	.001
Hypertension	251	311	.44
Unstable angina	288	307	.28
Previous AMI	697	1001	.001
Diseased vessels	2.91 ± 0.8	2.93 ± 0.8	.49
Previous CVA	149	174	.97

AMI, Acute myocardial infarction; *CVA*, cerebrovascular accident.

In case of CT evidence of recent stroke, the lesion size was measured by a ruler to the nearest one-half millimeter in 2 dimensions and multiplied by the thickness of the slice, according to a previously described method.[7,8] For multiple or irregular lesions the sum of the single ischemic areas was calculated. All neurologic measurements were prospectively entered in our computerized database.

Patient population. For the purpose of the present study, data collection ended in January 1997 and 4409 patients were included.

On the basis of the described preoperative and intraoperative screening, 2987 of the 4409 cases (67.7%) were assigned to the low-risk group, 743 cases (16.8%) were assigned to the moderate-risk group, and 679 cases (15.4%) were assigned to the high-risk group.

Because normothermic CPB was never used in the high- and moderate-risk groups (who were instead treated with dedicated surgical strategies) and to prevent any substantial difference in the preoperative characteristics of patients of different subsets, we decided to restrict the present analysis to the 2987 low-risk patients, excluding moderate- and high-risk cases. The first 1385 of these patients underwent an operation in which hypothermic CPB was used (hypothermic group), whereas the remaining 1602 cases underwent an operation in which normothermic systemic perfusion was used (normothermic group).

The main preoperative clinical and angiographic characteristics of patients of the hypothermic and normothermic groups are shown in Table I. The 2 groups were comparable with regard to most of the examined variables; significant differences were found only in the number of patients with dislipidemia or previous myocardial infarction.

Surgical technique. All the operations were performed by the same 5 surgeons who used standardized techniques. After median sternotomy and pericardiotomy, CPB was established by cannulating the right atrium and the ascending aorta. In the hypothermic group hypothermic systemic perfusion

Table II. *Operative data*

	Hypothermic group	*Normothermic group*	P *value*
Aortic crossclamp time (min)	53 ± 14	52 ± 16	.07
CPB time (min)	91 ± 14*	79 ± 18	.001
Bypass/patient	3.18 ± 0.3	3.21 ± 0.5	.05

*$P < .01$.

Table III. *Comparison between the clinical outcome and the extension of the cerebral lesion among patients who underwent an operation in which hypothermic versus normothermic CPB was used*

	Hypothermic group (n = 1385)	*Normothermic group (n = 1602)*	P *value*
Intraoperative stroke (n)	12	13	.97
Postoperative stoke (n)	3	3	.81
Total (%)	15 (1.0)	16 (0.9)	.96
Mean GOS score	3.66 ± 1.11	2.50 ± 1.59	.02
Mean CT extension of the ischemic lesion (mm^3)	5500 ± 1990	7200 ± 2000	.02

(28°C) and intermittent (every 30 minutes) antegrade cold (4°C) crystalloid cardioplegia were used; mean nasopharyngeal temperature in this group was 27.4 ± 0.9°C. Systemic rewarming was always initiated immediately before the beginning of the last anastomosis, and crossclamp removal was usually performed at a nasopharyngeal temperature of 30°C.

In contrast, in the normothermic group, normothermic systemic perfusion (≥34°C) was used, and myocardial protection was achieved by intermittent isothermic antegrade-retrograde blood cardioplegia; patients were actively rewarmed if their nasopharyngeal temperature failed below 34°C; the mean nasopharyngeal temperature in this group was 36.3 ± 0.8°C.

In both groups, mean arterial pressure during CPB was maintained between 50 and 70 mm Hg; volume infusion and/or vasopressors (phenylephrine) were used in case of hypotension (which occurred in 49.8% of patients in the normothermic group and in 10.1% in the hypothermic group; $P = .001$). Proximal and distal anastomoses were always performed during a single period of aortic crossclamping.

Main intraoperative data of patients of both groups are summarized in Table II.

Statistical analysis. Data are expressed as mean value ± SD.

Groups were compared by the χ^2 test for qualitative data, the unpaired Student *t* test for quantitative variables, and the Mann-Whitney *U* test for ordinal data.

For statistical analysis only the last GOS score assigned and the last CT scan performed were considered.

Table IV. *Comparison between the clinical outcome and the extension of the cerebral lesion among patients who underwent an operation in which hypothermic versus normothermic CPB was used in relation to the time of onset of the stroke*

	Hypothermic group	*Normothermic group*	P *value*
Intraoperative stroke (n)	12	13	
Mean GOS score	3.66 ± 1.23	2.15 ± 1.57	.01
Mean CT extension of the ischemic lesion (mm^3)	5600 ± 2000	7700 ± 1800	.01
Postoperative stroke (n)	3	3	
Mean GOS score	3.66 ± 0.57	4 ± 0	.36
Mean CT extension of the ischemic lesion (mm^3)	5100 ± 2000	5000 ± 890	.94

Results

Overall, 31 cases of perioperative stroke (25 intraoperative and 6 postoperative) were reported in the 2987 low-risk patients (1.0 %).

As shown in Table III, the prevalence of both intraoperative and postoperative stroke was not influenced by the CPB temperature used at operation (12 intraoperative and 3 postoperative strokes in the hypothermic group vs 13 intraoperative and 3 postoperative events in the normothermic group; $P = .96$).

However, the neurologic outcome assessed by the GOS was significantly worse in patients who underwent operation in which normothermic CPB was used (Table III). In fact, in the hypothermic group only 1 patient (6.6%) died, and in 10 cases (66.6%) the GOS score was more than 3. In contrast in the normothermic group, 8 patients died (50.0%), and in only 7 cases (43.7%) the GOS score was more than 3. Similarly, the mean volume of the ischemic area calculated at the CT scan was significantly more extended in the normothermic group (Table III).

Moreover, when the data was analyzed in relation to the time of occurrence of the brain damage (intraoperative versus postoperative), it is evident that the wide difference between the normothermic and hypothermic groups relied on the intraoperative (and not postoperative) events (an observation suggesting that an intraoperative factor should have accounted for the observed discrepancies).

In fact, the clinical outcome and the CT-shown extent of the brain lesion were similar among patients of the 2 groups who experienced a postoperative stroke, whereas both variables were significantly different when the intraoperative events were considered (Table IV).

Comment

Despite the wide diffusion of normothermia in the clinical practice, controversies still exist on the effect of normothermic CPB on the postoperative neurologic outcome. In fact, the major studies on this subject yielded opposite results (supporting or denying in turn the neurologic safety of normothermia)[1-4] so that to date a definitive clarification of this issue has not been achieved.

The present report suggests that the prevalence of neurologic events is similar between patients undergoing hypothermic or normothermic CPB and denies any effect of the CPB temperature on the prevalence of perioperative stroke.

However, the striking finding of our study is that, in the case of perioperative brain damage, the use of normothermic systemic perfusion is associated with a significantly more extended ischemic lesion and a worse neurologic outcome. In fact, in our experience more than 66% of patients (10/15 patients) of the hypothermic group received a GOS score at discharge of more than 3, and only 1 patient of this group (6.6%) died of stroke. In contrast, in the normothermic group 8 of the 16 patients (50.0%) died of the brain lesion, and only 7 patients of this group (43.7%) received a GOS score of more than 3; similarly, brain CT scans showed a significantly larger ischemic area in normothermic patients.

When analyzing these data in relation to the time of onset of the brain damage (intraoperative vs postoperative), the discrepancy between the hypothermic and normothermic groups becomes even more evident and both the clinical and CT *P* values pass from a moderate to high significance (Tables III and IV), supporting the hypothesis that an intraoperative factor should account for the observed differences. Because CPB temperature seems the most important intraoperative variable that differed between the 2 groups, the hypothesis that systemic hypothermia is the explanation for the better behavior of patients of the hypothermic group seems strongly supported.

In recent years, Craver and colleagues[9] already noted the better neurologic outcome of patients who experienced an intraoperative stroke in condition of hypothermic versus normothermic systemic perfusion; however, their observations were reported only anecdotally, and no information on the radiologic extension of the lesions was presented. Besides that, and despite the number of investigations performed on the effect of normothermia on the prevalence of cerebral complications in patients who underwent CABG, to date no study has correlated the clinical and CT severity of intraoperative stroke with the perfusion temperature used at operation.

Despite the widely known protective effect of hypothermia,[10-12] the physiopathologic explanation of what we observed is not immediate; indeed, transcranial Doppler examinations have shown that cerebral embolization is maximal during the phases of the operation that precede or follow systemic cooling (namely, aortic cannulation or crossclamp removal)[13] so that it has been hypothesized that the temperature management during CPB should not affect the postoperative neurologic outcome.[4]

However, cerebral microemboli are probably responsible for the subtle neuropsychologic changes that occur after cardiac surgical procedures[14] but are unlikely the cause of overt stroke, and data derived from transcranial Doppler studies should be applied with caution to patients who experience major intraoperative brain damage. Moreover, because it is known that a moderate degree of brain hypothermia can offer a substantial benefit in terms of brain protection from ischemic damage[15] and because the exact thermal gradients between peripheral and cerebral temperatures in the various phases of hypothermic and normothermic CPB and the difference in temperature between different areas of the brain (and more notably, between normoperfused and ischemic areas) have not yet been firmly established,[16,17] the conclusion that the CPB temperature does not influence the postoperative neurologic status cannot be accepted without major reservations.

On the basis of the present knowledge and of our observations, it is possible to hypothesize that hypothermic CPB has a neuroprotective effect sufficient to influence the recovery of cerebral neurons after an ischemic injury (and it seems conceivable that this effect is maximal in the borderline nonfunctional but viable and potentially salvageable penumbra) so that, once an intraoperative stroke has occurred, the extent of the ischemic area and consequent clinical manifestations are worse in case of normothermic systemic perfusion.

The results of our study should be interpreted in the light of its limitations. Although no major changes in the surgical and anesthesiologic management were introduced during the study period and all the data were prospectively collected, the comparison of 2 consecutive series of patients is obviously less rigorous than a prospective randomized trial. Moreover, because a perioperative stroke is a rare event, the overall number of cases is limited and our conclusions need to be confirmed in large multi-institutional trials involving a larger number of patients.

Despite that, the wide difference in both the neurologic outcome and the spatial extent of the brain lesion between the patients of the 2 groups who had an intraoperative stroke (but not a postoperative stroke) can hardly be explained on the basis of the simple chance and strongly suggests that the major intraoperative parameter, which varied between the 2 groups (systemic temperature), is the explanation for the observed discrepancies. In addition, the fact that our population was comprised of cases that, after a careful preoperative and intraoperative screening of the ascending aorta and carotid arteries, were judged at low risk of neurologic complications minimizes the role of patient-related factors and maximizes the effect of external variables (CPB temperature) on the extent of the intraoperative stroke.

In conclusion, this study shows that, when an intraoperative stroke occurs, the use of normothermic systemic perfusion results in a more extended ischemic area and is associated with a worse neurologic outcome; this observation opens new questions about the neurologic safety of normothermia. Large prospective randomized trials comparing the clinical effect of warm versus hypothermic systemic CPB on every single organ and postoperative complications are needed to objectively evaluate the advantages of normothermic systemic perfusion and to define its role and indications in the clinical practice.

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Appendix: Definitions

Neurologic complications

Intraoperative stroke was defined as a new focal neurologic deficit or coma associated with CT demonstration of recent ischemic cerebral lesion that became evident at the moment of the awakening from the anesthesia and lasted more than 24 hours.

Postoperative stroke was defined as a new focal neurologic deficit or coma lasting more than 24 hours and associated with CT evidence of recent ischemic cerebral lesion that occurred after a normal awakening from the anesthesia and a normal postoperative neurologic status.

Transient ischemic attack was defined as the onset (either at the awakening or after a normal postoperative period) of a new neurologic deficit lasting fewer than 24 hours and associated with normal brain CT.

Previous cerebrovascular events were defined as an anamnestic history of either overt stroke or reversible cerebral ischemic attacks.

Internal carotid artery disease was graded on the basis of the preoperative echo Doppler examination in *absent*, *slight* (monolateral or bilateral stenosis ≤50%), *moderate* (monolateral or bilateral stenosis between 50% and 80%), or *severe* (monolateral or bilateral stenosis ≥80%) disease. In cases of bilateral carotid artery stenoses of different degrees the classification was based on the most severe lesion.

Ascending aorta disease was graded according to Mills and Everson[18] in *absent*, *mild* (small diseased areas on the aorta that could easily be avoided with the aortic cannula and bypass grafts); *moderate* (disease extensive enough to cause concern for possible embolization, yet adequate soft disease-free areas could be found for cannulation or placement of bypass grafts); or *severe* (clearly significant circumferential disease that would necessitate aortic cannulation, aortic crossclamping, and placement of bypass grafts into diseased ascending aorta).

In cases in whom intraoperative ultrasonographic examination was used the ascending aorta and the proximal aortic arch were divided in 3 equal segments in the coronal plane (proximal, middle, and distal), and the atherosclerotic lesions were classified according to the criteria described by Wareing and colleagues[19]: *no disease*, *mild* (localized thickening ≤3 mm in the 3 segments), *moderate* (intimal thickening 3 to 5 mm in 1 or more segments), or *severe* (intimal thickening >5 mm in 1 or more segments and/or the presence of marked calcification, protruding or mobile atheroma, ulcerated plaques, thrombi, or circumferential involvement of most or all the ascending aorta) disease.

Neurologic outcome of patients who had a stroke was graded according to the GOS[6] as follows: 1, death; 2, persistent vegetative state; 3, severe disability; 4, moderate disability; and 5, good recovery.