

Hypothermic circulatory arrest with selective antegrade cerebral perfusion in ascending aortic and aortic arch surgery: A risk factor analysis for adverse outcome in 501 patients

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Objective: This study was undertaken to identify preoperative and intraoperative risk factors influencing outcome after operations requiring hypothermic circulatory arrest with selective antegrade cerebral perfusion in a single center.

Methods: Between November 1999 and March 2006, a total of 501 consecutive patients (median age 64 years, range 20–86 years, 320 male) underwent aortic arch surgery with moderate hypothermic circulatory arrest ($25^{\circ}\text{C} \pm 2^{\circ}\text{C}$) and additional selective antegrade cerebral perfusion (14°C) at our institution for various indications (256 aneurysms, 153 acute and 23 chronic type A aortic dissections, 66 other). Of these, 181 were emergency operations. Statistical analysis was carried out to determine risk factors for 30-day mortality as well as for temporary and permanent neurologic dysfunction.

Results: Overall mortality was 11.6%. Permanent neurologic dysfunction occurred in 48 patients (9.6%); temporary neurologic dysfunction was detected in 67 patients (13.4%). Multivariate analysis revealed age ($P = .001$, odds ratio 1.08), reoperation ($P = .006$, odds ratio 3.58), femoral arterial cannulation ($P = .004$, odds ratio 2.87), and cardiopulmonary bypass duration ($P < .001$, odds ratio 1.009) as risk factors for mortality. Permanent neurologic dysfunction was associated with preoperative renal insufficiency ($P = .029$, odds ratio 2.79) and operation time ($P < .001$, odds ratio 1.005), whereas temporary neurologic dysfunction occurred in patients with coronary artery disease ($P = .04$, odds ratio 2.29), emergency surgery ($P = .001$, odds ratio 4.09), and increasing hypothermic circulatory arrest duration ($P = .01$, odds ratio 1.015).

Conclusion: Moderate hypothermic circulatory arrest in combination with cold selective antegrade cerebral perfusion is an adequate tool for neuroprotection during aortic surgery. Nevertheless, the safety of this technique is limited for patients with long intraoperative durations, advanced age, and multiple comorbidities. This technique, which avoids profound core temperatures, has become an alternative to simple deep hypothermic circulatory arrest.

Increasing expertise in managing thoracic aortic diseases has been acquired during the last few years.¹⁻³ Nevertheless, neurologic complications after hypothermic circulatory arrest (HCA) for complex aortic arch procedures are still a matter for concern.⁴ Adjunct brain protection techniques have therefore been introduced during the last two decades.⁵⁻⁷ Selective antegrade cerebral perfusion (SACP) is probably the most promising tool for reducing morbidity and mortality.^{1,2} SACP has been applied worldwide with various modifications.^{1,5,6,8,9}

In recent studies, it has been shown that mortality and permanent neurologic dysfunction (PND) after aortic arch surgery are directly correlated with patient factors as

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Abbreviations and Acronyms

CPB	= cardiopulmonary bypass
HCA	= hypothermic circulatory arrest
PMD	= permanent neurologic dysfunction
SACP	= selective antegrade cerebral perfusion
TMD	= temporary neurologic dysfunction

well as the extent of operation. In contrast, it seems that the occurrence of temporary neurologic dysfunction (TND) is closely associated with the method of brain protection and the duration of HCA.^{1,2,10} The symptom complex of TND is associated with cognitive dysfunction and impaired quality of life.¹¹⁻¹³ In this study, we report on more than 500 patients who underwent operation during a 7-year interval in a single center with a standardized protocol for HCA and SACP.⁸

Materials and Methods

This retrospective study was approved by the institutional review board. All patients gave informed consent.

Patient Characteristics

Five hundred one consecutive patients who underwent aortic arch surgery with HCA and SACP from November 1999 to March 2006 in our department were included in the study. Median age was 64 years (range 20–86 years); 320 were male. One hundred ten patients (22%) had undergone previous cardiac or aortic operations. Further demographic and preoperative data are shown in Table 1.

Preoperative Management

All patients underwent standard preoperative examinations (chest radiography, electrocardiography, and blood tests) as well as computed tomographic scans or magnetic resonance imaging, as determined by pathology and urgent status.

All patients undergoing elective surgery underwent preoperative evaluation of their extracranial vessels with Doppler ultrasonography to exclude carotid artery stenosis or severe calcification and plaques, as well as pulmonary function tests for detection of chronic obstructive pulmonary disease (forced expiratory volume in 1 second <70%). Coronary angiography and echocardiography were also routinely performed: a restricted ejection fraction was defined as 35% or less. Glomerular filtration rate was estimated with the Cockcroft–Gault equation; impaired renal function was defined as less than 60 mL/min.

Anesthesia Management

Routine monitoring included 5-lead electrocardiography, a triple-lumen central venous catheter and 8.5F sheath in the internal jugular vein, a thermodilution catheter in select cases (eg, patients with severe pulmonary hypertension or impaired ejection fraction), invasive pressure monitoring in both radial arteries as well as the right femoral artery, pulse oximetry, blood gas values, and esophageal and bladder temperatures. Bilateral cerebral oxygen saturation was measured by noninvasive spectroscopy (INVOS; Somanetics Corporation, Troy, Mich).

TABLE 1. Demographic and preoperative data

	No.	%
No. of patients	501	100%
Characteristics		
Male	320	63.8%
Female	181	36.1%
Age (y, median and range)	64 (20–86)	
Body mass index >30 kg/m ²	98	19.6%
Previous thoracic surgery	110	22%
Marfan syndrome	16	3.2%
Status post thrombendarterectomy of the internal carotid artery	4	0.8%
Atrial fibrillation	54	10.8%
Smoking history	190	37.9%
Hypertension	380	75.8%
Hyperlipidemia	219	43.7%
Chronic obstructive pulmonary disease (forced expiratory volume in 1 s <70%)	93	18.6%
Peripheral arterial disease	18	3.6%
Coronary arterial disease	153	30.5%
Type 1 diabetes	6	1.2%
Dialysis	5	1%
Ejection fraction <35%	11	2.2%
Glomerular filtration rate <60 mL/min	97	19.3%
Indications		
Aneurysm	256	51.1%
Acute aortic dissection type A	153	30.5%
Chronic aortic dissection type A	23	4.6%
Other	66	13.2%
Emergency operations	181	36.1%

All patients received standard anesthesia for induction. For maintenance, all patients received sevoflurane at an end-tidal concentration of 0.5% to 2% and fentanyl. Thiopental (5 mg/kg · h) was infused continuously, with an addition bolus of 500 mg before HCA. A 2-mL/kg dose of mannitol (20%) and a 1000-mg bolus of methylprednisolone were also given. To achieve topical cooling, the head was packed in ice before HCA. Another dose of mannitol was given during reperfusion.

Cardiopulmonary Bypass Management

Alpha stat principles were used for arterial blood gas management. Hematocrit was maintained between 21% and 25% by hemodilution or administration of red blood cells. To minimize blood loss, 2 million IU of the kallikrein inhibitor aprotinin was given after HCA during reperfusion to avoid potential side effects of hypothermia. Duration of cooling was at least 30 minutes to ensure that it was uniform and thorough.

A separate single roller pump was used for blood cardioplegia (6°C–8°C) and SACP, with continuous measurement of flow rates and pressures. The perfusion temperature was adjusted to about 14°C; perfusion pressure was 40 to 60 mm Hg, which usually corresponds to flow rates of 400 to 650 mL/min. Potential vagaries of blood pressure were treated with papaverine or calcium antagonists in the brain perfusion. During rewarming, care was taken to avoid hyperthermia and high gradients between blood perfusion

temperature and core temperature, according to the suggestions of Ergin and Griep. ¹⁴

Surgical Technique

The proximal aorta and the aortic arch were approached through a median sternotomy. After systemic heparinization, the ascending aorta was cannulated in most cases. Alternatively, the left femoral artery was used (eg, in reoperative cases), according to the surgeon's preference. In most cases, venous return was established with a two-stage cannula placed in the right atrium. CPB was initiated, and the patient was cooled to the target temperature. A vent was placed in the left heart through the right superior pulmonary vein. Myocardial protection was achieved by administration of cold blood cardioplegia (6°C–8°C) with a separate roller pump, which was later used for SACP. After the anticipated HCA temperature was reached, cardiopulmonary bypass (CPB) was stopped, the aorta was opened, and the arterial cannula was removed. After exploration of the aortic arch, the patient was placed in Trendelenburg position, and two 15F retrograde cardioplegic catheters (RCSP MR 20; Medtronic, Inc, Minneapolis, Minn) were introduced under visual control into the innominate and left carotid arteries. After meticulous deairing, perfusion was started with a flow rate of 10 mL/(kg · min) and adjusted to maintain the pressure at the tip of the cannula between 40 and 60 mm Hg. In addition, the right radial artery pressure was continuously monitored. In cases of back flow, the left subclavian artery was occluded with a Fogarty catheter to avoid a steal phenomenon and achieve a bloodless surgical field. The arch was repaired according to the pathology and the surgeon's preference.

CPB was reestablished for rewarming in an antegrade fashion after the arch repair by direct cannulation of the graft and meticulous deairing of the supra-aortic vessels. During cooling and rewarming, other surgical procedures were performed, as determined by the concomitant pathology, to avoid extended CPB times.

Postoperative Management

After hemodynamic stabilization and achievement of minimal chest tube bleeding in the intensive care unit, no additional anesthetic drugs were given to allow evaluation of the gross neurologic status. Otherwise sedation was continued until hemodynamic stabilization and reduction of the fraction of inspired oxygen to 0.4.

Neurologic Evaluation

Analysis was focused on discriminating between PMD (frank strokes) and TND. Patients were considered to have PMD if they exhibited the onset of focal deficits postoperatively or were found to have a focal lesion confirmed by means of computed tomographic scanning or magnetic resonance imaging of the brain.

TND was defined according to Ergin and coworkers¹² as a symptom complex of postoperative confusion, agitation, delirium, prolonged obtundation, or transient parkinsonism with negative results on imaging of the brain. Patients with PND were excluded from analysis for TND. Patients with TND or PND were included in the statistical analysis even if they later died.

Statistical Analysis

Results are expressed as mean \pm SD, median and range, or percentage, as appropriate. Statistical analysis was performed with the Student *t* test or Pearson χ^2 test for categorical variables. Forward

stepwise logistic regression was used to discriminate risk factors for 30-day mortality, PND, and TND. The Kaplan–Meier survival estimate was used to analyze survival. Statistical differences in Kaplan–Meier survival estimates were determined with the log-rank test. Statistical analysis was performed using SPSS 14.0 software (SPSS Inc, Chicago, Ill) in cooperation with the Institute of Biometrics of Hannover Medical School.

Results

Intraoperative Data

Most patients (71%) underwent open distal anastomosis or hemiarch repair. Total arch repair was performed in the remaining 29%; 14% had some type of elephant trunk procedure (Table 2). Aortic valve surgery was performed in 67% cases; of these, 38% had reconstruction (eg, David I procedure).

In a few cases with aortic rupture, circulatory arrest was performed immediately after sternotomy because establishment of CPB was not possible. In these cases, cold SACP was administered after the opening of the aortic arch, and isolated crystalloid cardioplegia was given directly into the coronary ostia.

Adverse Outcome

Overall 30-day mortality was 11.6% (58 patients). PND occurred in 48 patients (9.6%), and TND was detected in 67 patients (13.4%). Twelve patients with PND (25%) died, compared with 5 patients with TND (7%; Figure 1). The overall incidence of severe adverse outcome (permanent stroke or death) was therefore 18.6%. The 30-day mortality was highly affected by preoperative urgency status: 92.2% versus 81.8% survival for nonemergency versus emergency (log-rank test $P < .001$).

Risk Factor Analysis

The Pearson χ^2 test and stepwise logistic regression were performed to identify independent risk factors for adverse outcome (30-day mortality, PND, TND). Of all tested factors, only age in addition to HCA and SACP times had a significant impact on each analyzed adverse event. TND was affected only by prolonged HCA and SACP, indicating its value as a marker for imperfect cerebral protection (Table 3).

HCA and SACP Times

To express the difference in HCA and SACP times between groups with and without adverse outcome, the mean times were plotted (Figure 2). The differences were statistically significant for all groups. For patients with PND, mean SACP time was 29 ± 21 minutes, compared with 22 ± 17 minutes for those without stroke ($P = .015$). Patients with TND had a mean HCA time of 27 ± 18 minutes, compared with 22 ± 18 minutes for those without neurologic disorders ($P = .038$).

TABLE 2. Intraoperative data and additional surgical procedures

	Mean ± SD	Range	No.	%
Operation time (min)	290 ± 99	123-936		
Cardiopulmonary bypass time (min)	184 ± 74	61-603		
Crossclamp time (min)	115 ± 43	25-283		
Hypothermic circulatory arrest time (min)	29 ± 21	7-138		
Selective antegrade cerebral perfusion time (min)	23 ± 18	3-95		
Urine bladder temperature (°C)	29 ± 2.3	19-37		
Esophageal temperature (°C)	25 ± 2.3	16-34.5		
Aortic arch surgery				
Proximal arch/open distal anastomosis/hemiarch			356	71.1%
Total arch			52	10.4%
Plus elephant trunk			35	7%
Plus frozen elephant trunk			36	7.2%
Other			21	4.2%
Aortic valve surgery			333	66.5%
Replacement			207	62.2%
Reconstruction			126	25.1%
David I procedure			95	19%
Mitral valve surgery			12	2.4%
Replacement			7	1.4%
Repair			5	1%
Coronary artery bypass grafting			117	23.4%
Intra-aortic balloon pump/extracorporeal membrane oxygenation			9	1.8%

Multivariate Analysis

Age and reoperation were the only preoperative independent risk factors for early mortality. With regard to intraoperative factors, femoral cannulation and CPB time appeared to be significant independent variables. PND was influenced by impaired renal function as well as operative time, indicating that strokes are strongly associated with the duration of the operation. TND was significantly higher in the emergency group and among patients who had concomitant coronary artery disease. As in previous studies, HCA duration was strongly correlated with the incidence of TND (Table 4).

Discussion

The best approach for protection of the brain during operations on the aortic arch is still a matter of controversy, even though during the last few years new cerebral protection techniques as well as cannulation sites have been introduced.^{3,5,7} McCullough and coworkers¹⁵ calculated a theoretic safe duration of HCA as long as 45 minutes at 10°C as the result of temperature-induced reductions in cerebral metabolism. Unfortunately, however, symptoms of TND occurred after 25 minutes, implying that HCA alone is not safe if extended times are necessary.¹²

From clinical as well as experimental data, it seems that providing antegrade flow to the brain is the most physiologically compatible way of providing cerebral protection.^{2,16-18} But the optimal temperature and the specific distribution regimen for antegrade cerebral perfusion are still a matter of concern and have been studied recently in animal models.^{19,20}

The rationale of providing cold blood to the brain is to combine the advantages of deep temperatures for the cerebrum with moderate temperatures for the rest of the body, with the Bachet technique,⁵ to avoid extended CPB times for prolonged rewarming. Harrington and coworkers²¹ showed in a clinical study that SACP may attenuate the cerebral metabolic deficits seen after HCA and concluded that concerns stemming from the increasing embolic load appear to be unsubstantiated.

To avoid deep HCA, which is associated with extended CBP times, we started to perform aortic arch surgery under

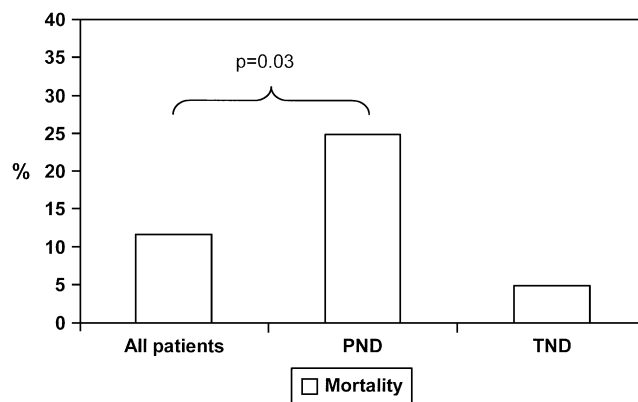


Figure 1. Mortality for entire cohort is plotted against patients dying after previous permanent neurologic dysfunction (PND) or temporary neurologic dysfunction (TND).

TABLE 3. Risk factor analysis for adverse outcome

Factor	N	P values		
		Mortality	PND	TND
Age(y)	501	.019	.038	.039
Acute aortic dissection type A	153	.002	NS	.015
Previous surgery	110	.035	NS	NS
Emergency	181	<.001	NS	.003
Status post stroke	36	.039	.006	NS
Peripheral vascular disease	18	.029	NS	NS
Glomerular filtration rate <60 mL/min	97	.002	NS	.043
Femoral arterial cannulation	71	<.001	NS	NS
Coronary artery bypass grafting	117	.033	NS	NS
Intra-aortic balloon pump/extracorporeal membrane oxygenation	9	.002	NS	NS
Operative time (min)		<.001	<.001	NS
Cardiopulmonary bypass time (min)		<.001	.001	NS
Crossclamp time (min)		.003	.006	NS
Hypothermic circulatory arrest time (min)		.003	.004	.013
Selective antegrade cerebral perfusion time (min)		.007	.017	.04

Age and times were included as continuous variables in the statistical model. *PND*, Permanent neurologic dysfunction; *TND*, temporary neurologic dysfunction; *NS*, not significant.

moderate HCA with the aid of cold SACP in 1999, according to a standardized protocol published in 2003.⁸ In this context, we recently showed with propensity score analysis that higher body temperatures had no adverse effects on mortality and morbidity. Furthermore, deeper temperatures were a risk factor for reexploration because of bleeding.²²

It is well known that a significant portion of atheromas are located in the descending aorta. For this reason, we tried to avoid cannulation of the femoral artery if possible. Direct cannulation of the ascending aorta or aortic arch is our standard approach for arterial CPB access, even in patients with acute aortic dissection type A.²³ The cannulation of the axillary or subclavian artery is another elegant option, especially when SACP is applied.³ Cannulation of the carotid artery has recently been introduced by Urbanski and coworkers.²⁴

We are comfortable with our technique of introducing perfusion catheters through the opened aortic arch in the innominate and left carotid artery under visual control. This technique is safe and easy to apply and is not associated with an additional microembolic load to the brain.²⁵ With this approach, both hemispheres of the brain are safely perfused, directly controlled by pressure and flow rates, and indirectly monitored by near-infrared spectroscopy. This issue is of special importance because Merkkola and coworkers²⁶ showed in a recent anatomic study that as many as 17% of patients are likely to have inadequate perfusion of the left hemisphere with purely right-sided inflow because of an incomplete circle of Willis.

The overall mortality rate of 11.6% in this study is comparable to the results of others, but the stroke rate of 9.6% is a matter for concern. In the literature, the incidence of stroke ranges between 4% and 6%.¹⁻³ It is not clear in all the studies

whether strokes were counted if the patient died during the initial hospital stay. This is important information, because our study showed a significant higher mortality rate among patients with PND than among the entire cohort, or even among patients with TND. It should be noted that this study includes a high proportion of patients who were operated on

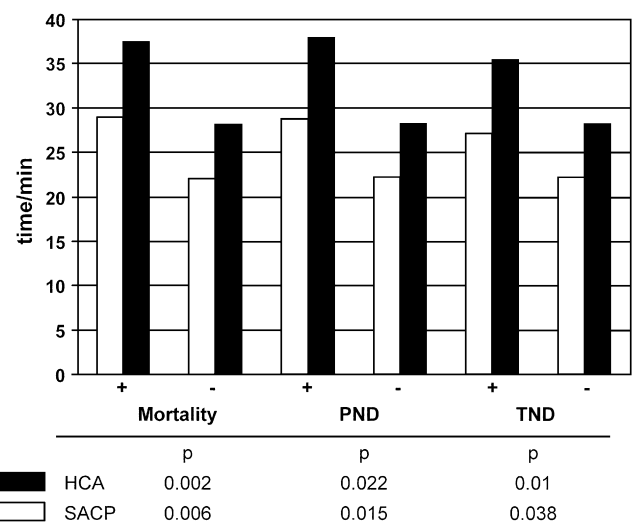


Figure 2. Average hypothermic circulatory arrest (HCA) time with corresponding selective antegrade cerebral perfusion (SACP) time in patients with (plus signs) and without (minus signs) adverse outcomes of mortality, permanent neurologic dysfunction (PND), and temporary neurologic dysfunction (TND). Statistical analysis was performed to show differences between groups with and without events.

TABLE 4. Multivariate analysis

Factor	P value	Odds ratio	95% Confidence interval
Mortality			
Preoperative			
Age	.001	1.08	1.03-1.13
Previous surgery	.006	3.58	1.49-8.60
Intraoperative			
Femoral arterial cannulation	.004	2.87	1.44-5.73
Cardiopulmonary bypass time	<.001	1.01	1.01-1.01
Permanent neurologic dysfunction			
Preoperative			
Glomerular filtration rate <60 mL/min	.029	2.79	1.16-6.75
Intraoperative			
Operative time	<.001	1.01	1.003-1.008
Temporary neurologic dysfunction			
Preoperative			
Emergency	.001	4.09	2.04-8.21
Coronary artery disease	.04	2.29	1.16-4.54
Intraoperative			
Hypothermic circulatory arrest time	.011	1.02	1.00-1.03

in emergency situations. Moreover, it is our policy to accept all patients for surgery, even if they require preoperative assisted ventilation or inotropic support, and even when their neurologic status is unknown. Previous studies have shown that stroke is strongly associated with patient- and disease-related factors as well as with duration of operation.^{1,2} In accord with these studies, our statistical analysis revealed age and a history of previous neurologic event, as well as operative times, as significant risk factors for stroke.

Years ago, symptoms of TND were considered harmless, because they resolved before discharge and computed tomographic or magnetic resonance imaging scans of the brain revealed no abnormalities. But Ergin and coworkers¹² showed that TND correlates significantly with poor performance on neuropsychologic tests at 1 postoperative week and is predictive of continued deficits in memory and motor function 6 weeks after surgery. Immer and coworkers¹³ showed a reduction of TND with the use of SACP during HCA. Patients treated with SACP had a higher quality of life during follow-up than did those with other methods of cerebral protection.

The detection of TND is controversial, however, with no standard test battery. The incidence of TND therefore ranges from 0% to 33%, mostly associated with long durations of HCA and additional brain protection techniques.^{2,12,27} In a recent study, Bucerius and associates²⁸ reviewed a large cohort of patients undergoing cardiac surgery in which the incidence of delirium, a symptom that is often seen after operations with CPB, was 8.4%. In this patient cohort, a history of cerebrovascular disease, peripheral vascular disease, atrial fibrillation, diabetes mellitus, left ventricular ejection fraction 30% or lower, preoperative cardiogenic shock, urgent opera-

tion, intraoperative hemofiltration, an operative time of at least 3 hours, and a high perioperative transfusion requirement were significantly associated with delirium. Protective against delirium were beating-heart surgery and younger patient age. With increasing expertise in managing thoracic aortic diseases, we have started to perform additional procedures more frequently, resulting in increased CBP times,^{29,30} which may contribute more than the cerebral protection protocol to an increased incidence of what appears to be TND.

Limitations

This was a retrospective study, with a high proportion of patients with previous operations, emergency status, and extensive surgery. Despite the heterogeneity of the cohort, we consider that reporting on patients operated in a single center with a standardized protection protocol may provide further insight into the problem of cerebral damage during aortic surgery. There is unquestionably still room for improvement in optimizing the specific technique of SACP.

Conclusions

Moderate HCA in combination with cold SACP is an adequate tool to prevent TND after aortic arch surgery. Nevertheless, with increasing intraoperative times, older patient age, and multimorbidity, the safety of this technique is limited. The major effect of SACP is to protect the cerebrum better by providing nourishment, but SACP also permits avoidance of profound whole-body hypothermia, with its potential for negative side effects.

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