Long-term neurodevelopmental outcomes in school-aged children after neonatal arterial switch operation

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Objective: Neurodevelopmental status of children between 8 and 14 years of age after neonatal arterial switch operation for transposition of the great arteries has not previously been systematically evaluated.

Methods: Within a longitudinal study, 60 unselected children operated on as neonates with combined deep hypothermic circulatory arrest and low-flow cardiopulmonary bypass were reevaluated at the age of 7.9 to 14.3 years (mean $\pm$ SD 10.5 ± 1.6 years). Clinical neurologic status and standardized tests to assess gross motor function, intelligence, acquired abilities, language, and speech were carried out, and the results were related to preoperative, perioperative, and postoperative status, to management, and to neurodevelopmental status at a mean age of 5.4 years.

Results: Neurologic and speech impairments were evidently more frequent (27% and 40%, respectively) than in the general population. Intelligence and socioeconomic status were not different ($P = .29$ and $P = .11$), whereas motor function, acquired abilities, and language were reduced ($P \leq .04$ for each). Overall rate of developmental impairment in one or more domains was 55%, compared with 26% at age 5.4 years. Multivariable analysis showed that severe preoperative acidosis and hypoxia predicted reduced motor function (mean deficit 52.7 points, $P < .001$), whereas longer bypass duration predicted both neurologic (odds ratio per 10 minutes of bypass duration 1.8, $P = .04$) and speech (odds ratio per 10 minutes of bypass duration 1.9, $P = .02$) dysfunction, and perioperative and postoperative cardiocirculatory insufficiency predicted neurologic (odds ratio 6.5, $P = .04$) and motor (mean deficit 6.8 points, $P = .03$) dysfunction.

Conclusions: The neonatal arterial switch operation with combined circulatory arrest and low-flow bypass is associated increasingly with age, with reduced neurodevelopmental outcome but not with cognitive dysfunction. In our experience, the risk of long-term neurodevelopmental impairment after neonatal corrective cardiac surgery is related to deleterious effects of the global perioperative management and to special adverse effects of prolonged bypass duration. Severe preoperative acidosis and hypoxia and postoperative hemodynamic instability must be considered as important additional risk factors.

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The arterial switch operation (ASO) to correct transposition of the great arteries (TGA) in neonates has been globally accepted as the method of choice because of low perioperative and postoperative mortality and good midterm results with respect to the cardiologic outcomes and endurance of these children. Concern, however, has been raised by the occurrence of neurologic dysfunction and developmental sequelae that may accompany neonatal cardiac surgery supported by continuous low-flow cardiopulmonary bypass (CPB), either isolated or combined with deep hypothermic cardiocirculatory arrest (DHCA).

Previously, we reported midterm results of cognitive and motor development in preschool- and school-aged children at a mean age of 5.4 years after neonatal ASO performed between 1986 and 1992 with combined DHCA and low-flow CPB.¹ Our patient group had reductions in neurologic and fine and gross motor functions, vocabulary, and acquired abilities, but was within the reference range for formal intelligence testing. In contrast, a second group of children who had undergone ASO between 1994 and 1995 and were assessed in our institution at a mean age of 3.6 years revealed remarkably less developmental impairment than seen in our older children.² Midterm results of the Boston Circulatory Arrest Study at the age of 4 years after neonatal ASO³ demonstrated reduced performance of the full cohort with respect to several domains of testing, including neurologic and motor functions, intelligence, and language. Use of circulatory arrest was associated with worse outcomes in motor and speech functions than seen with the preponderant use of low-flow CPB. Recent results of a developmental evaluation of children aged 3 to 5 years after corrective infant cardiac surgery, including patients after neonatal ASO, add to the evidence of risks concerning neurologic and cognitive function but do not support the assumption of increased risk using cardiac arrest.⁴

Limited conclusions can be drawn from these findings with respect to the impact of the different bypass strategies and their concomitant modalities and the impact of preoperative and postoperative risk parameters on final developmental status after neonatal corrective cardiac surgery. The aim of this study was therefore to evaluate for the first time long-term neurologic, motor, cognitive, academic, language, and speech development 10 years after ASO by reassessment of our uniform group of children with TGA.¹ Further information should be obtained as to which factors in preoperative, perioperative, and postoperative management influence long-term outcome and to what degree neonatal surgery performed with DHCA and with CPB by itself may contribute to neurologic and developmental impairment in older school-aged children and adolescents.

Methods

Patient population

Between March 1986 and February 1992, 96 neonates with TGA underwent ASO. In 1995, at a mean age of 5.4 years, 77 children (86.5% of the survivors) were evaluated with respect to their cognitive and motor development.¹ In 2000, at a mean ($\pm$ SD) age of 10.5 ± 1.6 years (range 7.9–14.3 years), 60 of them were reevaluated. The remaining 17 patients were evaluated with a questionnaire. There were no further late deaths. All patients, except those with cerebral palsy, had normal endurance capacity, and none received any cardiac-related medication.

Our study was approved by the ethical medical committee of the Aachen University of Technology, Aachen, Germany, and written informed consent was obtained from the patients and their parents. The study comprised a longitudinal comparison with our former evaluation¹ and was designed as a case series with published controls and prognostic factor analyses. The study group consisted of 60 unselected children (77.9% of the survivors), 46 (76.7%) of whom were male and 14 (23.3%) of whom were female. Socioeconomic status of the families⁵ was not different from that of a general population ($P = 0.11$, χ^2 test). Seventy-three percent had a simple TGA, 17% in addition had an unimportant ventricular septal defect, 3% had a ventricular septal defect closed during ASO, and 7% had a coarctation of the aorta corrected later. Eighty-five percent of the neonates had undergone atrial balloon septostomy, and all had been treated with prostaglandin E₁ before the operation.

Questionnaires for the 17 patients who did not participate in the present follow-up study were completed by the parents and by the treating pediatricians and pediatric cardiologists; participation was determined mainly by the distance of the family's residence from our institution. The children who did not participate in the study were not different from the study patients with respect to socioeconomic background.

Surgical Management and Perfusion Methods

ASO under conditions of DHCA and combined low-flow CPB was performed in our institution by two surgeons (B. J. Messmer, S. H. Daebritz) according to a standardized technique that was based on the Lecompte modification. The CPB circuit included a roller pump, a disposable membrane oxygenator, and an arterial filter. Cooling and rewarming were carried out with a heat exchanger. After induction of general anesthesia, core cooling on CPB was instituted under full-flow conditions ($2.7 \text{ L}/[\text{m}^2 \text{ body surface area} \cdot \text{min}]$) to reach an esophageal temperature of 14°C to 17°C ($15.1^\circ\text{C} \pm 1.0^\circ\text{C}$). The temperature of the priming fluid was 20°C to 22°C . The priming solution consisted of a pH-balanced crystalloid solution containing 5% glucose and packed red blood cells to achieve a hematocrit value of the circulating volume of 0.25. The duration of core cooling ranged from 7 to 20 minutes (10.8 ± 2.7 minutes). Duration of DHCA ranged from 51 to 67 minutes (60.0 ± 3.1 minutes), and the aortic crossclamping period ranged from 53 to 96 minutes (65.7 ± 8.1 minutes). The surgical procedure was completed under low-flow conditions with a perfusion rate of $0.7 \text{ L}/[\text{m}^2 \text{ body surface area} \cdot \text{min}]$. Rewarming and preparation for weaning from CPB were achieved under full-flow conditions. Total CPB, including core rewarming time, comprised 42 to 98 minutes (63.4 ± 13.7 minutes). During CPB the pH-stat

TABLE 1. Preoperative, perioperative, and postoperative courses: risk factors for neurodevelopmental outcome

Risk factor	Result	Definition
Perinatal asphyxia (No.)	8/60 (13.3%)	Apgar score <7 after 5 min
Severe preoperative acidosis and hypoxia (No.)	7/60 (11.7%)	pH value <7.2 in umbilical venous blood (n = 3); severe postasphyxia syndrome with organ failure and cerebral seizures (n = 2); repeated severe cyanosis caused by intracardiac mixing problems (n = 2)
Age at operation (d, mean $\pm$ SD)	7.1 $\pm$ 5.1	
Duration of DHCA (min, mean $\pm$ SD)	60.0 $\pm$ 3.1	
Duration of CPB (min, mean $\pm$ SD)	63.4 $\pm$ 13.7	
Duration of aortic crossclamping (min, mean $\pm$ SD)	65.7 $\pm$ 8.1	
Duration of core cooling on CPB (min, mean $\pm$ SD)	10.8 $\pm$ 2.7	
Temperature at initiation of DHCA ($^{\circ}$ C, mean $\pm$ SD)	15.1 $\pm$ 1.0	
Additional ventricular septal defect patch closure (No.)	2/60 (3.3%)	
Perioperative and postoperative cardiocirculatory insufficiency (No.)	10/60 (16.7%)	Low cardiac output* despite adequate filling pressures and inotropic and vasodilatory therapy
Perioperative and postoperative resuscitation events (No.)	4/60 (6.7%)	Pharmacologic or mechanical resuscitation necessary
Postoperative intraventricular cerebral hemorrhage (No.)	4/60 (6.7%)	Evaluation by cranial ultrasonography before operation; 4 h after operation; 1, 2, and 3 d after operation; and 1 and 2 wk after operation; persistence of intraventricular cerebral hemorrhage-like findings 2 weeks after operation, according to Sigler et al ⁶
Perioperative and postoperative clinical seizures (No.)	2/60 (3.3%)	
Age at neurodevelopmental testing (y, mean $\pm$ SD)	10.5 $\pm$ 1.6	
Socioeconomic status	$P = .11$ † vs published control values	Social classification of family by main breadwinner's profession, according to Moore and Kleining ⁵

*Low cardiac output was clinically estimated by means of arterial pressure (target value for mean pressure 45 mm Hg), central venous pressure (target value 5-7 mm Hg), diuresis (target value >1.5 mL/[kg body weight $\cdot$ h]), capillary refill time, and skin temperature.

† P value calculated by comparison of frequencies; socioeconomic status represents an ordinal scale.

method was used, correcting arterial carbon dioxide tension (P_{aCO_2}) to the patient's hypothermic temperature to maintain a pH value of 7.40. At the beginning of CPB, phentolamine (0.1 mg/kg) and (since 1990) sodium nitroprusside were added for vasodilation. Dexamethasone (3 mg/m² body surface area) was given before sternotomy. The age at repair for the study group ranged from 2 to 39 days (7.1 $\pm$ 5.1 days). Two patients were older than 12 days.

Risk Factors for Neurodevelopmental Outcome

The patients' charts were carefully reviewed with respect to perioperative management and preoperative, perioperative, and postoperative complications. For the analysis of the influence of cerebral risk factors on later outcome, a list of 15 definite variables, available in all cases, was considered (Table 1).⁶

Neurologic Examination

Complete clinical neurologic status was evaluated by an examiner experienced in neuropsychiatric examinations (H. H. Hövels-Gürich). Results were classified as normal or impaired. Impairment was categorized as mild (no functional impairment), moderate (functional impairment requiring therapy), or severe (dependence on

continued assistance). Disorders were subclassified into 7 types of dysfunction (more than one of which could be present in a single case) as follows: disorders of either head shape and growth or cranial nerves, motor dyspraxia, ataxia, sensory dysfunction, palsy, and seizures (clinical or electroencephalographic) during the last 12 months⁷⁻⁹ (Table 2). Isolated nonparalytic strabismus was not classified as neurologic disorder and was excluded from further analysis in this setting.

Developmental Testing

All assessments were conducted in the whole cohort by the same examiner during the morning hours in our institution. The applied tests are normalized for age to have a mean ($\pm$ SD) of 100 $\pm$ 15. Dysfunction was diagnosed when standard scores were below the simple SD (standard scores <85).

The Kiphard and Schilling Body Coordination Test¹⁰ was administered to assess standard scores of gross motor function (motor quotient, MQ).

The Kaufman Assessment Battery for Children¹¹ was performed to evaluate overall standard score of general intelligence (IQ). A second test block of the same battery was undertaken to evaluate acquired abilities (learning, academic knowledge). Three

patients (5%) who were older than 12.5 years were assessed according to the norms for children aged 12.0 to 12.5 years.

Language was assessed by evaluating standard scores of expressive (combination of chosen items comprising subtests 4, 12, 14, and 15 of the Kaufman Assessment Battery for Children) and receptive language (combination of chosen items comprising subtests 7, 13, 14, and 16 of the Kaufman Assessment Battery for Children).

Developmental test results in the patients were compared with the published results of an age-matched healthy, German-speaking population, on which the tests or their German adaptations are based. The incidence of abnormal results in a reference population is by definition 16% (14% below the simple SD but above the double SD and 2% below the double SD).

Examination of Speech

At the time of assessment, all children had normal hearing, as evaluated by tone threshold audiometry. Speech was assessed with the Oral and Speech Motor Control test¹² and selected items of the children's battery of the Mayo Tests of Speech and Oral Apraxia,¹³ both adapted to the German language by our neurolinguists (W.H. and R.S.). In addition, we performed the German version of the Auditory Closure subtest of the Illinois Test of Psycholinguistic Abilities (ITPA),¹⁴ as well as the Test of Auditory Analysis Skills¹⁵ in a German adaptation (W.H. and R.S.), both of which assess auditory comprehension and phonation. Patients were classified as having a normal or an impaired overall speech function according to the total functional score (TFS)¹² comprising 56 items (maximum 112 points) with respect to function of volitional oral movements, articulation, phonation, and coordination of speech. The cutoff point for an impaired speech function was set at a score of less than 110 points, which is equivalent to the median value reported by Robbins and Klee.¹² Reliability of this classification was verified by relating the additional speech assessments to the TFS.

Statistical Analysis

Results are expressed as mean $\pm$ SD or as numbers with percentages. For comparison of mean values, *t* tests were applied; for comparison of frequencies, the χ^2 test was used. For intergroup comparison of clinical variables, the nonparametric Mann-Whitney *U* test was applied. For comparison of variables at specific times of assessment within a group, the paired nonparametric Wilcoxon test was used. The Spearman rank correlation coefficient was assessed for correlation of independent parameters, and the Fisher exact test was used for the analysis of contingency tables. An α adjustment for repeated measures was done according to the Bonferroni-Holm method. To study the impact of risk factors on neurodevelopmental outcome parameters, a multivariable analysis was applied with a generalized linear model for continuous outcome parameters and a logistic regression model for binary outcome parameters with 8 independent risk factors, 4 of which were statistically significant in corresponding univariate analysis: severe preoperative hypoxia, durations of DHCA and CPB, perioperative and postoperative cardiocirculatory insufficiency, perioperative and postoperative resuscitation events, perioperative and postoperative clinical seizures, postoperative intraventricular cerebral hemorrhage, and socioeconomic status.

TABLE 2. Neurologic dysfunction after ASO, as evaluated in 60 children

	No.	%
Total with dysfunction	16	26.7
Grade of dysfunction		
Mild	9	15
Moderate	5	8.3
Severe	2	3.3
Type of dysfunction*		
Head shape and growth	5†	8.3
Cranial nerves	6‡	10
Motor dyspraxia	8§	13.3
Ataxia	5	8.3
Sensory	0	0
Palsy	3	5
Seizures	3	5

*More than one type of dysfunction possible in one child.

†Microcephaly, *n* = 3; macrocephaly, *n* = 1; hydrocephalus with ventriculo-peritoneal shunt, *n* = 1.

‡Dysfunction of palate or tongue, *n* = 5; nystagmus, *n* = 1.

§Developmental fine or gross motor coordination disorder.

||Quadriplegia or hemiplegia.

Multivariate discrimination analysis was performed to test the discriminatory power of neurologic and speech functional scores with respect to combined dysfunctions in the domains of motor, cognitive, and academic abilities.

Statistical analysis was performed with the SPSS for Windows software, version 10.0 (SPSS GmbH Software, München, Germany), and with the Statistical Analysis System, version 8.0 (SAS Institute, Inc, Cary, NC). The term *significant* was used to indicate purely statistical, not clinical, significance.

Results

Neurologic Status

Sixteen children (26.7%) had neurologic abnormalities, 56% of which were considered mild. Rates, grades, and types of dysfunctions are described in Table 2. Neurologic dysfunction was found to be associated with lower MQ ($P < .001$) and IQ ($P = .001$) and with poorer outcomes for acquired abilities ($P = .005$) and receptive language ($P < .001$).

Developmental Evaluation

Gross motor dysfunction was found in 26.7% of the patients (11.7% below the simple SD and 15% below the double SD for MQ). Reduced formal intelligence was diagnosed in 18.3% (15% below the simple SD and 3.3% below the double SD for IQ), and dysfunction in academic knowledge (acquired abilities) was diagnosed in 23.3% (18.3% below the simple SD and 5.0% below the double SD). Expressive language was found to be reduced in 18.3% (18.3% below the simple SD) and receptive language was found to be

TABLE 3A. Speech outcome after ASO: Distribution of TFS

TFS	Patients	
	No.	%
Normal		
112	7	11.7
111	13	21.7
110	16	26.7
Total	36	60
Impaired		
109	6	10
108	4	6.7
107	2	3.3
106	1	1.7
105	3	5
104	1	1.7
103	1	1.7
96	2	3.3
95	1	1.7
91	1	1.7
65	1	1.7
54	1	1.7
Total	24	40

reduced in 21.6% (18.3% below the simple SD and 3.3% below the double SD).

Speech Evaluation

Dysfunction of speech was found in 24 of the patients (40%). Distribution of TFS is shown in Table 3A. Significant relationship of TFS classification to the results of the nonparametric Mayo Test for Apraxia of Oral Movements, the ITPA Auditory Closure subtest, and the Test of Auditory Analysis Skills confirmed the reliability of this categorization (Table 3B). None of the speech test results were found to be dependent on age at testing (TFS, Spearman correlation coefficient 0.01, $P > .2$, Mayo, Spearman correlation coefficient 0.05, $P > .2$, ITPA, Spearman correlation coefficient 0.2, $P > .2$, Test of Auditory Analysis Skills, Spearman correlation coefficient 0.18, $P = .17$). Speech dysfunction was also found to be related to lower MQ and IQ and to poorer outcomes for acquired abilities and expressive and receptive language (Table 3B).

Test Results in Comparison With Norms for Children

Patients were considered either as the whole group or as subgroups comprising patients without or with neurologic damage to evaluate whether neurologic dysfunction might be associated with other developmental dysfunctions. The results of the standardized developmental tests to evaluate MQ, IQ, acquired abilities, and expressive and receptive language are shown in Table 4. Children without neurologic dysfunction did not differ from healthy children in acquired abilities and expressive and receptive language, and they even tended to be better than the control group with respect

to MQ and IQ; this, however, could have been due to chance. Children with neurologic dysfunction had significantly poorer than reference performances in all test domains. Patients of the whole group showed lower test results than seen in the control group for all items except IQ.

Discriminatory Power of Neurologic and Speech Functional Scores

Eighty-one percent of patients with neurologic dysfunction also had speech impairment, whereas 54% of patients with speech impairment showed simultaneous neurologic dysfunction. By means of both scores, it was possible to discriminate patients with combined dysfunction in the domains of motor, cognitive, and academic abilities from those without dysfunction. In multivariate discrimination analyses, patients with neurologic dysfunction were also found to be impaired in the other domains with a sensitivity of 77% (percentage of correctly identified patients with impairment) and not impaired with a specificity of 86% (percentage of correctly identified patients without impairment). Children with speech dysfunction were also found to be impaired in the other domains with a sensitivity of 76% and not impaired with a specificity of 72%. Patients with neurologic and speech dysfunction or with either one of these could be classified as impaired in motor, cognitive, and academic abilities with sensitivities of 77% and 78%, respectively, and not impaired with specificities of 83% and 85%, respectively, indicating that neurologic and speech dysfunctions were strong indicators of global developmental impairment.

Overall Developmental Impairment and Longitudinal Comparison

Summarizing all examination results, 45% of the study patients were within the test limits with regard to motor, cognitive, academic, language and speech development, as well as neurologic status, whereas 55% showed developmental impairment in one or more domains of evaluation, 13.3% were found to have isolated impairment of speech, and 6.7% revealed dysfunctions in all domains of child development considered in this study.

Compared with our previous results of the same study group examined at a mean age of 5.4 years,¹ acquired abilities were now found to be significantly poorer ($P = .02$), whereas differences in IQ may have been due to chance ($P = .10$). The rate of neurologic dysfunction significantly increased, from 9.1% to 26.7% ($P = .001$), mainly as a result of additional patients showing motor dyspraxia (fine or gross motor coordination disorder). In total, the proportion of patients without any dysfunction decreased from 74% to 45% (Figure 1).

The questionnaires of the 17 patients who did not participate in this study provided percentages of normal and reduced neurodevelopmental outcomes similar to those

TABLE 3B. Speech outcome after ASO: Relationship of TFS to additional speech and developmental tests

	TFS normal (n = 36)	TFS impaired (n = 24)	P value*
Oral movements, Mayo test	152.8 ± 4.5	144.7 ± 12.4	.02
Receptive speech, ITPA Auditory Closure subtest	26.5 ± 3.1	22.9 ± 5.1	.006
Receptive speech, Test of Auditory Analysis Skills	12.1 ± 1.3	10.2 ± 2.9	.005
MQ	102.5 ± 18.8	78.2 ± 31.6	.001
IQ	104.0 ± 14.0	91.3 ± 14.0	.001
Acquired abilities	102.1 ± 15.4	86.1 ± 14.3	.001
Expressive language	99.7 ± 12.8	92.0 ± 10.8	.02
Receptive language	102.3 ± 10.6	89.2 ± 11.5	<.001

Values are mean ± SD, standard deviation.

*P values calculated by Mann-Whitney *U* tests for comparison of normal and impaired TFS.

TABLE 4. Developmental outcomes after ASO compared with norms for healthy children

Developmental test	Standard score (mean ± SD)	Results (%)			P value†
		Normal*	Abnormal		
			<−1 SD	<−2 SD	
MQ					
All patients (n = 60)	92.8 ± 27.3	73.3	11.7	15	.02
Patients without neurologic damage (n = 44)	103.5 ± 13.6	88.6	11.4	—	.05
Patients with neurologic damage (n = 16)	63.4 ± 33.7	31.3	12.5	56.2	<.001
IQ					
All patients (n = 60)	98.9 ± 16.8	81.7	15.0	3.3	.29
Patients without neurologic damage (n = 44)	103.1 ± 13.7	90.9	9.1	—	.07
Patients with neurologic damage (n = 16)	87.3 ± 13.3	62.5	25.0	12.5	<.001
Acquired abilities					
All patients (n = 60)	96.2 ± 15.2	76.7	18.3	5.0	.04
Patients without neurologic damage (n = 44)	99.4 ± 6.7	81.8	15.9	2.3	.40
Patients with neurologic damage (n = 16)	85.3 ± 12.1	62.5	25.0	12.5	<.001
Expressive language					
All patients (n = 60)	96.9 ± 12.6	81.7	18.3	—	.04
Patients without neurologic damage (n = 44)	98.3 ± 13.0	90.9	9.1	—	.19
Patients with neurologic damage (n = 16)	91.8 ± 9.7	56.2	43.8	—	<.001
Receptive language					
All patients (n = 60)	97.6 ± 12.5	78.4	18.3	3.3	.08
Patients without neurologic damage (n = 44)	100.6 ± 11.6	88.6	9.1	2.3	.36
Patients with neurologic damage (n = 16)	86.5 ± 9.5	49.9	43.8	6.3	<.001

*Normal considered to be above −1 SD.

†P values calculated by comparison of mean values, normal and abnormal results relative to age-matched healthy children (standard score ± SD = 100 ± 15).

among the participants of the study: neurologic dysfunction, 27%; developmental impairment, 40%; and overall proportion of impaired patients, 47%.

Influences of Preoperative, Perioperative, and Postoperative Risk Factors on Neurodevelopmental Outcomes

Comparison of children with and without impairment revealed that severe preoperative acidosis and hypoxia were related to neurologic and speech dysfunctions ($P < .001$ and $P = .001$, respectively, Mann-Whitney *U* test) and to poorer

outcomes with respect to MQ, IQ, acquired abilities, and receptive language ($P = .001$, $P = .004$, $P = .02$, and $P = .007$, respectively). Duration of CPB was associated with neurologic and speech dysfunctions ($P = .001$ and $P = .003$, respectively) and inversely correlated with MQ (Spearman correlation coefficient -0.27 , $P = .04$). Perioperative and postoperative cardiocirculatory insufficiency were related to neurologic dysfunction ($P = .02$, Mann-Whitney *U* test). Socioeconomic status was also negatively associated with neurologic and speech functions ($P = .02$ and $P = .009$, respectively) and was inversely correlated

Figure 1. Diagram illustrating percentages of dysfunction in different domains of assessment as evaluated in 60 patients.

with standard scores of intelligence and acquired abilities (Spearman correlation coefficient -0.56 , $P < .001$, and Spearman correlation coefficient -0.60 , $P < .001$, respectively), as well as with receptive and expressive language (Spearman correlation coefficient -0.65 , $P < .001$, and Spearman correlation coefficient -0.53 , $P < .001$, respectively). The additional 11 risk factors (Table 1) were not found to be significantly related to any outcome parameters ($P > .2$ for each).

In the models of multivariable analysis, 7 dependent outcome parameters were considered, each of them related to 8 risk factors as specified previously. Among those, the model was able to confirm 4 variables as independent risk factors with respect to neurodevelopmental outcome. More detailed information is given in Tables 5A and 5B. The presence of severe preoperative acidosis and hypoxia predicted reduced motor function (MQ mean deficit 52.7 points). Duration of CPB was able to predict both neurologic and speech dysfunction (risk elevation 1.8 and 1.9 times, respectively, per 10 minutes of CPB). The presence of perioperative and postoperative cardiocirculatory insufficiency predicted neurologic dysfunction (risk elevation 6.5 times) and motor dysfunction (MQ mean deficit 6.8 points). Socioeconomic status was an independent risk factor for reduced IQ, acquired abilities, and expressive and receptive language.

Discussion

Our data are based on a homogeneous group of neonates with TGA in whom preoperative, perioperative, and post-

operative care was conducted according to standardized protocols. Longitudinal follow-up of developmental status 10.5 years after neonatal ASO was prospectively evaluated in a high percentage (86.5%) of surviving patients. Of these patients, 77.9% were examined with an extensive test battery; the remaining 22.1% were evaluated with a questionnaire. Similar percentages of impairment obtained with both assessment procedures suggest that the neurodevelopmental status of our study group is representative of the outcome of the whole cohort. By means of univariable and multivariable analyses, the outcome data were correlated with retrospectively collected preoperative, perioperative, and postoperative variables.

Neurodevelopmental Outcomes

Neurologic status. We found marked impairment of clinical neurologic status at age 8 to 14 years after neonatal ASO relative to healthy children and to the results of the same group 5 years ago.¹ The longitudinal increase of neurologic impairment (27%) was due to a higher prevalence of patients with developmental motor coordination disorders, or so-called “soft sign neurology,”^{8,9,16} rather than to cerebral palsy or organic motor coordination disorders caused by a central or peripheral neurogenic lesion. These soft neurologic signs could not be detected in the previous study because of the earlier developmental stage of the children. Although neurologic dysfunction was mostly mild, clinical relevance of these findings is underlined by significant correlation with motor, cognitive, academic, and psychosocial impairment (Arch Dis Child, in press) in our

TABLE 5A. Associations between cerebral risk factors and neurodevelopmental outcomes: Binary outcomes

	Neurologic dysfunction	Speech dysfunction
Severe preoperative acidosis and hypoxia <i>P</i> value	>.2	>.2
Duration of CPB (per 10 min) Odds ratio 95% confidence interval <i>P</i> value	1.8 1.0-3.1 .04	1.9 1.1-3.3 .02
Perioperative and postoperative cardiocirculatory insufficiency Odds ratio 95% confidence interval <i>P</i> value	6.5 1.1-38.3 .04	>.2
Socioeconomic status <i>P</i> value	>.2	>.2

Odds ratios, 95% confidence intervals, and *P* values were calculated by a logistic regression for the effects of severe preoperative acidosis and hypoxia, duration of CPB, perioperative and postoperative cardiocirculatory insufficiency, and socioeconomic status (5 categories) with respect to binary outcomes.

TABLE 5B. Associations between cerebral risk factors and neurodevelopmental outcomes: Continuous outcomes

	MQ	IQ	Acquired abilities	Expressive language	Receptive language
Severe preoperative acidosis and hypoxia Mean deficit 95% Confidence interval <i>P</i> value	52.7 35.4 to 69.9 <.001	17.3 5.8 to 28.8 .12	17.2 0.2 to 34.1 >.2	8.9 −4.1 to 21.8 >.2	14.6 2.1 to 27.2 >.2
Duration of CPB <i>R</i> ² <i>P</i> value	0.52 >.2	0.42 >.2	0.41 >.2	0.35 >.2	0.50 >.2
Perioperative and postoperative cardiocirculatory insufficiency Mean deficit 95% Confidence interval <i>P</i> value	6.8 −14.9 to 28.6 .03	7.7 −4.9 to 20.2 >.2	3.3 −9.8 to 16.3 >.2	4.5 −6.8 to 15.9 >.2	2.8 −8.4 to 13.9 >.2
Socioeconomic status <i>R</i> ² <i>P</i> value	0.52 >.2	0.42 .001	0.41 <.001	0.35 .007	0.50 <.001

Mean deficits, 95% confidence intervals, and *P* values were calculated by a generalized linear model for the effects of severe preoperative acidosis and hypoxia and of perioperative and postoperative cardiocirculatory insufficiency with respect to continuous outcomes. *R*² and *P* values were calculated by a generalized linear model for the effects of duration of CPB and socioeconomic status with respect to continuous outcomes.

study group. Our incidence of neurologic impairment was in a range similar to rates reported in other studies for definite neurologic abnormalities among children after neonatal ASO,^{3,17} although it was markedly higher than in cohorts operated on later, in 1994 to 1995.^{2,4} This may at least in part be due to improved preoperative management, which has been found to exert a significant influence on neurodevelopmental outcome. It must be noted, however, that the children operated later on were younger at examination.

Motor function. Gross motor dysfunction, as judged on the basis of a standardized assessment (MQ), was found to be more prevalent among our patients (27%) than in the general population. This figure is comparable to the frequency of gross motor impairment in our cohort at the age

of 5.4 years and to the results in the Boston study at the age of 4 years.³ The presence of gross motor dysfunction according to MQ showed a high overlap with neurologic abnormalities.

Intelligence. Formal intelligence, as based on IQ assessment, was not reduced relative to healthy children. This finding is consistent with the previous results of our study group¹ and with the results of our recent cohort of younger children,² whereas intelligence considerably below population norms after neonatal ASO has been demonstrated in other reports.^{3,4,17}

Academic achievement. By means of formal testing of acquired abilities, we demonstrated (consistent with another report after neonatal ASO¹⁷) significantly reduced outcomes

in age-adapted learning and knowledge relative to the test norms and to the results of the same cohort 5 years ago.

Language and speech. Expressive and receptive language were found to be poorer than population norms among our patients. Speech outcome assessed by the TFS, comprising oral nonspeech functions as well as expressive speech functions (articulation, phonation and coordination), was markedly reduced relative to healthy children.¹⁸ Normal auditory test results demonstrated that this finding could not be attributed to hearing deficits. Rather, general motor dysfunction was present in 40% of the speech-impaired children. In addition, disabilities of central integration appeared to contribute to our high rate of speech dysfunction (40% of the cohort), as suggested by strong correlations of TFS with performance in tests of receptive speech and language. This is underlined by the prevalence of a quite high rate of children with isolated speech impairment (13% of the cohort) without neurologic disorder, in contrast to a minority of children with neurologic disorder who did not have accompanying speech impairment (5% of the cohort). A high prevalence of speech and language dysfunction was also demonstrated in the Boston cohort.³ In that study as well as in ours, these dysfunctions were strongly associated with motor, cognitive, and academic disabilities, as well as with behavioral and social problems. Therefore speech and language dysfunctions are an important indicator of global developmental impairment.¹⁹⁻²¹

Overall impairment. According to the data discussed previously, the increase in detection rate of developmental impairment in one or more domains of assessment (55% vs 26% 5 years ago) is due mainly to the high incidence of neurologic and speech and language disorders, which are more easily detected in older than in younger children.

Risk Factors for Neurodevelopmental Outcomes

The factors influencing neurodevelopmental outcome after neonatal cardiac surgery are complex, involving the interactions of preoperative, perioperative, and postoperative parameters.^{22,23} The independent risk factors for neurodevelopmental dysfunction found in this study are discussed here.

Socioeconomic status. In our study group, which represented an even level of socioeconomic status relative to the German population,⁵ low socioeconomic status predicted poorer outcome in all cognition-related domains of evaluation as intelligence, academic achievement, and language. This is consistent with similar associations observed in other studies.^{3,17} The fact that academic achievement and language in the group as a whole were below expected population norms, however, suggests influences of additional factors.

Preoperative factors. The structural and functional immaturity of the cerebral circulation predisposes the neonate toward acquired cerebrovascular lesions, such as intracra-

nial hemorrhage and hypoxic-ischemic injury.²² In addition to the well-known general risk of low arterial oxygen saturation in children with cyanotic heart lesions such as TGA, situations of particularly severe preoperative hypoxia, such as were documented in some of our patients before surgery, have a negative impact on later speech and motor functions. Children with TGA represent a group without prevalent risk of genetic abnormality with respect to morbidity of the central nervous system²⁴ and therefore appear particularly appropriate for investigation of preoperative influences on developmental sequelae after neonatal cardiac surgery. The high incidence of neurobehavioral abnormalities in neonates documented before cardiac surgery and persisting in most after surgery²⁵ underlines the importance of preoperative brain injury for later developmental outcome. In our study, the outcome of motor development was primarily predicted by severe preoperative acidosis and hypoxia.

Perioperative and postoperative factors. Although acute manifestations of neurologic injury in the early postoperative period are often transient, they may be predictive of increased long-term neurodevelopmental dysfunction.²⁶ The risk for brain injury comprises disturbances in post-CPB cerebral perfusion, intrinsic vasoregulation, and cardiocirculatory function.²³ In our study, cardiocirculatory insufficiency, defined as low cardiac output situations resistant to intensive care treatment in the early postoperative period, was found to be an independent risk factor for later neurologic and motor disorders. Postoperative clinical seizures, evident in as many as 15% of neonates after cardiac surgery,^{27,28} have been found to be associated with reduced developmental impairment after ASO.^{3,29} In our study group, however, no correlation could be detected between the occurrence of clinically detected seizures and later development. This is consistent with our previous results on the same study group at age 5.4 years¹ as well as on our younger cohort² and may be due at least in part to the low incidence of clinical postpump seizures in our patients, among whom postoperative electroencephalography was not routinely performed.

Low-flow cardiopulmonary bypass. The technique of vital organ support during cardiac surgery in our institution includes a combination of low-flow CPB and DHCA. The risks of low-flow CPB comprise the exposure to cerebral embolic injury, cerebral hypoperfusion, and global inflammatory response continuing into the postoperative period.³⁰⁻³² In this study, longer duration of CPB was detected as an independent risk factor for poorer outcomes in neurologic and speech functions at age 10.5 years after ASO, whereas it had marginally increased the risk of intellectual impairment at the age of 5.4 years.¹ A recent report on the possibly deleterious effects of CPB on intelligence of patients after surgical closure of atrial septal defect versus those after interventional closure (device implantation) un-

derlines the necessity of a critical attitude with respect to current CPB strategies.³³

Children who needed additional patch closure of a ventricular septal defect, usually associated with longer support times, have been found to be at increased risk for poorer developmental outcomes.^{3,34} We could not confirm this observation, probably because of the small number of patients with that constellation.

Deep hypothermic cardiocirculatory arrest. DHCA leads to prolonged complete cerebral ischemia, including impairment of cerebral metabolism and vascular autoregulation.^{22,35} Predominant exposure to DHCA, as opposed to predominant use of low-flow CPB, was associated with worse outcomes in motor and speech development at the age of 4 years after neonatal ASO,³ whereas the institution of cardiac arrest and its duration did not affect neurologic and cognitive outcomes in a group of preschool-aged children after infant heart surgery.⁴ In this study, multivariable analysis did not point to DHCA duration, although longer than usual, as an independent risk factor for adverse neurodevelopmental outcome, consistent with our previous findings.^{1,2} This underlines results from animal studies, in which neurologic impairment did not occur until circulatory arrest times exceeded 60 minutes.³⁶

Other aspects of intraoperative management. Adequate degree and duration of the cooling period are important to reach the profoundly hypothermic brain temperatures that lead to sufficient reduction of cerebral metabolism.³⁷ Too-rapid cooling may exert adverse effects on cognitive functions.³⁸ Although duration of cooling on CPB in our patients was shorter than recommended, this factor did not have a negative impact on developmental outcome.

There is evidence that cerebral hyperthermia of 2°C or 3°C above core temperatures in children after CPB, as measured by jugular venous bulb temperature, typically occurs in the perioperative period after termination of CPB, inducing the risk of neurologic sequelae caused by hypoxic-ischemic lesions.^{36,39,40} Conflicting evidence exists concerning the pH management during CPB. Whereas the pH-stat strategy was found preferable in the postoperative period,^{22,41,42} use of the alpha-stat versus the pH-stat acid-base strategy during reparative infant cardiac surgery was not related to either improved or impaired neurodevelopmental outcomes 1 year after surgery.⁴³ Experimental data recently proved pH-stat CPB management in combination with DHCA to be superior to alpha-stat CPB with respect to neurologic outcome.⁴⁴ In our institution, the pH-stat method was always used.

Limitations

In this study the number of patients for multivariable analysis was somewhat limited. Therefore statistical power to identify predictors of developmental delay was limited to those with high associations.

Conclusions

Our study points out that developmental impairment 10 years after neonatal ASO with combined DHCA and low-flow CPB, as performed in our institution, was more prevalent than in both the general population and the same study group at the age of 5 years. Reduced cognitive function according to formal intelligence testing, however, was not observed.

In our experience, the risk of long-term neurodevelopmental impairment after neonatal corrective cardiac surgery is related to the deleterious effects of the global perioperative management and to special adverse effects of prolonged CPB duration. Severe preoperative acidosis and hypoxia and postoperative hemodynamic instability must be considered as important additional risk factors.

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