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ORIGINAL ARTICLE

Mortality and neurodevelopmental outcome at 1 year of age comparing hybrid and Norwood procedures

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CONGENITAL

Abstract

OBJECTIVES: Neonates with hypoplastic left heart syndrome (HLHS) are at risk of high mortality and neurodevelopmental morbidity. As an alternative to Norwood-type stage I palliation, the hybrid procedure has been developed. It consists of bilateral pulmonary artery banding, catheter-based stenting of the arterial duct and balloon atrioseptostomy and delays open-heart surgery. Thus, it may be associated with a better outcome. The aim of this study was to determine the mortality and neurodevelopmental outcome in patients with HLHS and other univentricular heart (UVH) defects treated with hybrid or Norwood procedures.

METHODS: Thirty-one children (18 males) with HLHS and other UVH defects undergoing Norwood or hybrid procedure between 2004 and 2008 were consecutively enrolled. Mortality and neurodevelopmental outcome at 1 year of age were determined.

RESULTS: One-year mortality was 36% (31% in the hybrid vs. 39% in the Norwood group, $P = 0.71$). Predictors of mortality were lower birth weight ($P = 0.02$), older age at first procedure ($P = 0.02$) and smaller size of ascending aorta ($P = 0.05$). Overall, median psychomotor development index (PDI) and mental development index (MDI) of the Bayley Scales of Infant Development II were lower than the norm of 100 [PDI 57 (49–99), $P < 0.001$; MDI 91 (65–109), $P = 0.002$]. No effect of surgical treatment on neurodevelopmental outcome was found. Predictors of impaired motor outcome were length of hospital stay (LOHS) ($P = 0.01$), lower body weight at second procedure ($P = 0.004$) and female sex ($P = 0.01$). Predictors of impaired cognitive outcome were longer mechanical ventilation time ($P = 0.03$), intensive care unit stay ($P = 0.04$) and LOHS ($P < 0.001$), respectively.

CONCLUSIONS: Mortality at 1 year of age is comparable between patients undergoing hybrid and Norwood procedures. Early neurodevelopmental outcome is significantly impaired in patients with both HLHS and other UVH defects. Multicentre randomized studies are needed to determine the long-term neurodevelopmental outcome of children treated with the hybrid procedure.

Keywords: Congenital heart defects • Hypoplastic left heart syndrome • Norwood operation • Cardiopulmonary bypass • Neurocognitive deficits • Hybrid procedure

INTRODUCTION

Norwood-type stage I–III palliation constitutes the standard of care in the majority of patients with hypoplastic left heart syndrome (HLHS) and other functionally univentricular heart (UVH) defects associated with systemic outflow tract obstructions with aortic arch hypoplasia and coarctation [1, 2]. Advances in the peri- and intraoperative management have decreased surgical as well as interstage mortality [3, 4]. Nevertheless, these patients are still at particular risk for neonatal morbidity, including brain injury and subsequent neurodevelopmental sequelae [5, 6].

The hybrid procedure has been developed as an alternative to Norwood-type stage I palliation combining catheter-based and surgical techniques [7, 8]. Bilateral pulmonary artery banding together with catheter-based stenting of the arterial duct and balloon atrioseptostomy controls pulmonary blood flow and provides a reliable systemic cardiac output through the patent arterial duct as well as an unrestricted interatrial blood flow [9]. Thus, the hybrid procedure delays cardiopulmonary bypass to the age of 3–5 months, at which age the comprehensive stage I and II procedure can be performed. This may lead to a reduction in neonatal and neurodevelopmental morbidity and mortality.

Therefore, we analysed the mortality as well as the neurodevelopmental outcome at 1 year of age in patients with HLHS and UVH defects treated with the hybrid and Norwood procedures in a prospectively enrolled cohort.

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MATERIALS AND METHODS

Study design

This study is part of a prospective longitudinal clinical cohort study on neurodevelopmental outcome and quality of life of children operated for congenital heart disease (CHD). The study has been approved by the Institutional Review Board of the University Children's Hospital Zurich, and written informed consent has been obtained from the parents or legal guardians.

Patient population

All consecutive patients born between April 2004 and July 2008 with the diagnosis of HLHS and UVH were eligible. Patients' inclusion criteria were main cardiac diagnosis of HLHS and other UVH combined with systemic outflow tract obstruction including aortic arch hypoplasia with severe aortic coarctation undergoing open-heart surgery with Norwood-type stage I palliation or hybrid procedure at our centre.

The decision on the preferred treatment strategy was made patient-per-patient in an interdisciplinary conference incorporating the complete treatment team with paediatric cardiology, cardiac surgery, intensive care medicine and anaesthesia. The treatment strategy was afterwards presented to the parents for their final agreement. In our institution, exclusion criteria for the hybrid procedure were severe aortic coarctation, hypoplasia of the transverse aortic arch and the ascending aorta (defined by a minimum size of the ascending aorta <2 mm) as well as restrictive foramen ovale and restricted pulmonary vein drainage.

Hybrid procedure

All procedures were performed under general anaesthesia. After induction of anaesthesia, median sternotomy was performed, and pulmonary arteries were banded bilaterally with a 3 mm long Goretex tube (body weight <3 kg, 3 mm diameter tube and body weight >3 kg, 3.5 mm diameter tube). The tube was lengthwise incised, wrapped around the left and right pulmonary arteries and secured with interrupted sutures [8]. For the catheter-based intervention, a 5 Fr sheath was placed and fixed in the lateral wall of the right atrium by the surgeon. Self-expanding bare metal stents (Sinus Repo, Optimed Co., Ettlingen, Germany) were used for the arterial duct stenting, serially covering the complete duct backwards from the descending aorta to the pulmonary artery under fluoroscopic guidance. The diameter of the stents was chosen at least 1 mm larger than the size of the descending aorta. Atrial septal defects were dilated using a 12 mm diameter Tyshak balloon dilatation catheter (Numed, Inc., Hopkinton, NY, USA). In two patients, HLHS was combined with only moderate aortic coarctation and consecutive mild restriction of aortic backflow, not fulfilling exclusion criteria for hybrid procedure; therefore, the aorta was stented during hybrid procedure using balloon expandable stents (Palmaz Blue, Cordis Co., Johnson & Johnson, Miami, FL, USA). A modified right-sided Blalock–Taussig (BT) reverse shunt was installed between main pulmonary artery and brachiocephalic trunk during the hybrid procedure in one patient with double inlet left ventricle (DILV) and severe hypoplasia of the aortic arch. In one patient with prenatally diagnosed HLHS and restrictive foramen ovale, atrioseptectomy was performed at the first day of life under cardiopulmonary bypass together with bilateral banding of the pulmonary arteries. The patient was then transferred to the catheterization laboratory for duct stenting.

Surgical management

Norwood-type stage I palliation. After median sternotomy in general anaesthesia, the surgeon performed a Damus–Kaye–Stansel anastomosis and a right-modified BT shunt or a right ventricle-to-pulmonary artery shunt. The aortic arch was reconstructed with xenopericard, and atrioseptectomy was performed under hypothermic cardiopulmonary bypass with selective cerebral perfusion. In eight patients, a 3.5 mm right-modified BT shunt was performed, and eight patients received a 5 mm and two patients a 6 mm right ventricle-to-pulmonary artery shunt.

Norwood-type stage II palliation. Twelve patients underwent Norwood-type stage II palliation at an age of 3–5 months. The shunt was resected, and bidirectional cavopulmonary anastomosis was performed under moderate hypo- or normothermic cardiopulmonary bypass in general anaesthesia. If necessary, the aortic arch and/or the pulmonary arteries were enlarged.

Comprehensive stage I and II palliation. In the case of preceding hybrid procedure in the neonatal period, comprehensive stage I and II palliation was performed at approximately 3–5 months of age in 10 patients. This procedure combines classical Norwood-type stage I and II procedures. Therefore, after median sternotomy, under general anaesthesia, the pulmonary artery bandings and the ductal stent/s were removed, and thereafter, Damus–Kaye–Stansel anastomosis together with aortic arch reconstruction and cavopulmonary anastomosis and patch enlargement of the pulmonary arteries and atrioseptectomy were performed under hypothermic cardiopulmonary bypass.

Cardiopulmonary bypass

For cardiopulmonary bypass, we used alpha-stat blood gas management and a pump flow rate at 100–150 ml/kg/min to achieve a mean arterial pressure of 40–50 mmHg. Norwood-type stage I palliation and comprehensive stage I and II procedures were performed under moderate hypothermia (nasopharyngeal temperature 22–28° C). Norwood-type stage II palliation was performed either under moderate hypothermia or under nearly normothermia (nasopharyngeal temperature 32–35°C). We performed regional cerebral perfusion with a pump flow rate maintained at 30–50 ml/kg/min and a target arterial pressure around 50–60 mmHg, measured in the right radial artery. Modified ultrafiltration at the end of cardiopulmonary bypass was performed in all patients.

Neurodevelopmental outcome

A standardized neuromotor examination was performed by an experienced neurodevelopmental paediatrician (B.L.) before the second procedure and at the age of 1 year. The assessment was modified after Prechtl [10] and included a neuromotor score

(NMS) (range 0–18, 0 was defined as normal and 18 as severely abnormal). All clinical examinations were performed under stable haemodynamic conditions, and children were not ventilated. Additionally, at the age of 1 year, children were examined with the Bayley Scales of Infant Development II [11]. This test provides a psychomotor development index (PDI) and a mental development index (MDI).

Statistical analysis

Analyses were performed using SPSS 16 (SPSS Inc., Chicago, IL, USA). Pre-, intra- and postoperative variables were related to mortality and outcome parameters (NMS, MDI and PDI) using Mann–Whitney *U*-test for continuous variables and Fisher's exact test for dichotomous variables. For the comparison of scores with the norm, we applied a one-sample *t*-test. To compare the change in NMSs between 3 months and 1 year, the Wilcoxon signed-rank test was applied. A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

Patient population

Thirty-seven patients (21 males) with HLHS and other UVH defects were eligible. Of these, six children were not surgically treated either because they died before surgery ($n = 3$) or they underwent comfort care ($n = 3$). Of the remaining 31 patients (18 males), 18 were treated with Norwood and 13 with hybrid procedure. Cardiac diagnoses included classical HLHS ($n = 24$), unbalanced atrioventricular septal defect (AVSD) with left ventricular hypoplasia ($n = 1$), double outlet right ventricle (DORV) with left ventricular hypoplasia ($n = 2$) and DILV ($n = 4$). Patients with DORV or unbalanced AVSD underwent hybrid procedure. Two patients with DILV were operated by the Norwood procedure and two by hybrid procedure. No genetic or malformation syndrome was present in the included patients. After birth, all patients received prostaglandin E2 infusion. Before surgery, patients were spontaneously breathing ($n = 28$, 90%) or intubated ($n = 3$, 10%). Reasons for intubation after birth were transfer to our hospital in one patient (extubated before Norwood I) and cardiogenic shock due to missed prenatal diagnosis in two patients who died early after their first surgical procedure (one underwent Norwood stage I and one hybrid procedure). The patient characteristics and perinatal and perioperative variables are presented in Table 1, and details of surgical and anatomical characteristics and neurodevelopmental outcome at 1 year of age are presented in Table 2.

One-year mortality

Overall, 11 patients died before the age of 1 year. Patients died early (<30 days, $n = 5$), late (>30 days, $n = 3$) after surgery or at home during interstage ($n = 3$). One patient died during late postoperative course of septicaemia due to an accidental

Table 1: Comparison of perinatal and perioperative variables for patients undergoing hybrid and Norwood procedures

Patients, $n = 31$	Norwood group 18	Hybrid group 13	*P*-value[a]	Survivors 20	Deceased 11
Male/female	10/8	8/5	1.0	14/6	4/7
Apgar 5 min	9 (7–10)	9 (8–9)	0.37	9 (8–10)	9 (7–9)
Prenatal diagnosis	9 (50%)	9 (69%)	0.46	13 (65%)	5 (45%)
Gestational age (weeks)	38 (35–40)	38 (38–41)	0.19	38 (37–41)	38 (35–40)
Birth weight (kg)	3.1 (2.1–4.2)	2.9 (2.2–3.9)	0.23	3.2 (2.4–4.2)	2.8 (2.1–3.8)
Birth head circumference (cm)	34.5 (30–37)	34 (30.5–36.2)	0.47	34 (32–36)	32.3 (30–37)
Antegrade flow in ascending aorta at birth	5 (28%)	7 (58%)	0.14	9 (47%)	3 (27%)
Diameter of the ascending aorta (mm)	3.0 (1.9–6.7)	4.3 (2.7–6.5)	0.05	4.7 (1.9–6.7)	3.5 (2–4.6)
Cardiac diagnosis: HLHS/others[b]	16/2	8/5	0.10	15/5	9/2
Age at first procedure (days)	5.5 (2–52)	5 (0–7)	0.23	4 (0–52)	7 (3–11)
Body weight at first procedure (kg)	3.2 (2.1–4.1)	3.0 (2.2–3.9)	0.33	3.2 (2.6–4.1)	2.9 (2.1–4.1)
Bypass time (min) during first procedure	191 (140–325)	–		–	–
Aortic clamp time (min) during first procedure	122 (35–157)	–		–	–
Mechanical ventilation (days) after first procedure	5 (2–26)	3 (1–11)	0.15	4 (1–15)	6 (2–26)
Length of ICU stay (days) after first procedure	11 (5–39)	8 (2–15)	0.12	10 (2–39)	11 (6–31)
Length of hospital stay (days) after first procedure	31 (15–90)	35 (13–204)	0.31	32 (13–204)	32 (30–34)
Age at second procedure (days)	131 (64–180)	130 (44–162)	0.57	132 (64–180)	83 (44–135)
Body weight at second procedure (kg)	5.2 (3.6–7.0)	5.4 (2.7–7.1)	0.88	5.4 (3.6–7.1)	4.1 (2.7–5.3)
Bypass time (min) during second procedure	111 (65–283)	242 (143–373)	0.01	225 (65–285)	143 (75–373)
Aortic clamp time (min) during second procedure	107 (72–141)	143 (83–194)	0.31	91 (0–194)	83 (0–194)
Mechanical ventilation (days) after second procedure	1.5 (0–6)	2 (0–24)	0.52	1 (0–6)	–
Length of ICU stay (days) after second procedure	5 (2–14)	5 (2–29)	0.45	5 (2–16)	–
Length of hospital stay (days) after second procedure	14.5 (11–46)	30 (12–49)	0.06	18 (11–49)	–

Results are presented as median and ranges or in number and percent.
[a]Mann–Whitney *U*-test for continuous variables and χ^2 with Fisher's exact test for dichotomous variables.
[b]Other cardiac diagnoses are DILV in four, DORV in two and unbalanced AVSD in one patient.

Table 2: Overview of surgical and anatomical characteristics and 1-year outcome of surviving patients after hybrid and Norwood procedures

Patient	Procedure	Cardiac diagnosis, size of ascending aorta, flow in ascending aorta	Risk factors	Reinterventions	PDI	MDI
1	Norwood	HLHS: AA/MA, 2.7 mm, anterograde flow		None	50	66
2	Norwood	HLHS: AS/MA, 4.0 mm, retrograde flow		None	57	102
3	Norwood	HLHS: AA/MA, not available, retrograde flow	Restrictive foramen ovale	First balloon dilatation and stenting re-CoA Second re-balloon dilatation of stent in CoA Third surgical removal of stent, patch enlargement CoA	na	105
4	Norwood	HLHS: AA/MA, 2.5 mm, retrograde flow		None	77	96
5	Norwood	HLHS: AA/MA, 6.0 mm, retrograde flow		First stenting LPA stenosis Second restenting LPA stenosis (after stent removal during Norwood II) Third balloon dilatation LPA stent	50	65
6	Norwood	HLHS: AS/MS, 5.0 mm, anterograde flow	Restrictive foramen ovale	None	72	93
7	Hybrid	HLHS: AA/MS, 6.3 mm, retrograde flow	Restrictive foramen ovale	First stenting restrictive foramen ovale Second surgical rebanding LPA and RPA	53	74
8	Hybrid	HLHS: AA/MS, 4.0 mm, retrograde flow		First stenting PDA restenosis, stenting CoA Second dilatation restrictive ASD Third surgical patch enlargement RPA and LPA stenosis	73	84
9	Hybrid + stent in CoA	HLHS: AS/MA, 5.0 mm, anterograde flow		First balloon dilatation of RPA and LPA stenosis	65	88
10	Hybrid + septectomy with CPB	HLHS: AS/MA, 4.3 mm, retrograde flow	Restrictive foramen ovale	First surgical loosening PA bandings Second coiling MAPCA	86	94
11	Hybrid	HLHS: AS/MS, 6.5 mm, anterograde flow		First stenting restrictive ASD Second stenting LPA stenosis, coiling venovenous collateral	90	97
12	Norwood	DILV, D-TGA, VSD, IAA-B, 5.5 mm, anterograde flow		First balloon dilatation residual CoA	81	109
13	Hybrid	DILV, L-TGA, 2.5 mm, anterograde flow		First stenting LPA stenosis	99	102
14	Norwood	HLHS: AS/MS, 6.0 mm, retrograde flow	Restrictive foramen ovale	None	56	82
15	Hybrid	DORV, VSD, hypoplastic LV, 6.0 mm, anterograde flow		None	54	96
16	Hybrid	HLHS: AA/MS, 2.8 mm, retrograde flow		First balloon dilatation restrictive ASD	57	86
17	Norwood	HLHS: AA/MA, <2 mm, retrograde flow		First balloon dilatation CoA	<50	78
18	Hybrid+BT-shunt	DILV, D-TGA, 6.3 mm, anterograde flow		First balloon dilatation right PA banding Second coiling venovenous collateral, stenting left PA stenosis, coiling MAPCAs	50	71
19	Norwood	DILV, L-TGA, 6.7 mm, anterograde flow	Restrictive foramen ovale	None	57	99
20	Norwood	HLHS: AA/MA, <2 mm, retrograde flow		None	<50	70

AA: aortic atresia; AS: aortic stenosis; ASD: atrial septal defect; CoA: aortic coarctation; CPB: cardiopulmonary bypass; d-TGA: dextro-transposition of the great arteries; IAA: interrupted aortic arch; LPA: left pulmonary artery; L-TGA: levo-transposition of the great arteries; LV: left ventricle; MA: mitral atresia; MAPCA: major aortopulmonary collateral artery; MS: mitral stenosis; na: not assessed; PA: pulmonary artery; PDA: patent ductus arteriosus; RPA: right pulmonary artery; VSD: ventricular septal defect.

intestinal perforation during change of percutaneous endoscopic gastrostomy tube. Another patient died of ongoing myocardial failure despite early Fontan procedure to reduce ventricular volume overload at the age of 10 months. One-year mortality was 36% (31% in the hybrid group vs. 39% in the Norwood group, $P = 0.71$). Of the 20 surviving patients (HLHS $n = 15$ and

UVH $n = 5$), 11 underwent Norwood stage I and 9 hybrid procedure.

Perioperative morbidity during first year of life

The duration of the combined bypass times after hybrid and comprehensive stage I and II, and Norwood-type stage I and II palliation, respectively, was shorter in the hybrid group with 250 (143–373) min than in the Norwood group with 293 (205–466) min ($P = 0.06$). Combined mechanical ventilation times were also shorter in the hybrid group with 6 (1–28) days vs. 8 (2–17) days ($P = 0.70$) as well as the median duration of intensive care unit (ICU) stays after both procedures with 16 (6–35) days in the hybrid group vs. 19 (8–43) days in the Norwood group ($P = 0.56$). Median combined length of hospital stays (LOHS) did not differ between the two treatment groups. One patient in the hybrid group stayed 204 days in hospital; he could not be discharged due to complex psycho-social problems. Patients undergoing Norwood procedure had less reinterventions (surgery and interventional heart catheterization) during the first year of life than those who underwent hybrid procedure [median: 0 (0–4) in the Norwood group vs. 2 (0–8) in the hybrid group; $P = 0.001$].

Neurodevelopmental outcome at 3 months and 1 year of age

At a median age of 3 (range 1–6) months, before the second procedure, 19 children were examined. Median NMS was comparable between the Norwood group and the hybrid group [4 (1–10) vs. 4 (1–9); $P = 0.64$]. At a median age of 12 (range 10–15) months, all 20 surviving children were examined. NMS for both groups improved ($P = 0.03$) between 3 and 12 months of age, and at 1 year, median NMSs were similar between Norwood and hybrid groups (Fig. 1).

At 1 year of age, median MDI for both groups was 91 (range 65–109), significantly lower than the norm ($P = 0.002$), but comparable between both treatment groups [Norwood 93 (65–109) vs. hybrid 88 (71–102), $P = 1.0$] (Fig. 2). Only children in the Norwood group had an MDI below 70 [Norwood $n = 2$ (18%) vs. hybrid $n = 0$ (0%), $P = 0.5$].

Median PDI was 57 (range 49–99), significantly lower than the norm ($P < 0.001$). Median PDI was slightly lower, but not significantly in the Norwood group compared with the hybrid group [Norwood 56.5 (49–81) vs. hybrid 65 (50–99), $P = 0.18$] (Fig. 3). The rate of children with a PDI below 70 was similar in both groups [Norwood $n = 7$ (64%) vs. hybrid $n = 5$ (56%), $P = 0.60$].

We did not find any significant difference in the neurodevelopmental outcome parameters (NMS, MDI and PDI) between patients with HLHS and UVH nor between patients with univentricular right ventricle (HLHS, DORV and unbalanced AVSD) and univentricular left ventricle (DILV) (all $P > 0.1$).

The one patient who received a BT shunt during the hybrid procedure had an MDI of 71 and a PDI of 50. The other patient with HLHS and restrictive foramen ovale who underwent cardiopulmonary bypass to perform atrioseptectomy together with hybrid procedure had an MDI of 94 and a PDI of 86.

Predictors of mortality

Lower birth weight ($P = 0.02$), older age at first procedure ($P = 0.02$) and smaller size of the ascending aorta ($P = 0.05$) were predictors of mortality during first year of life. All other perinatal

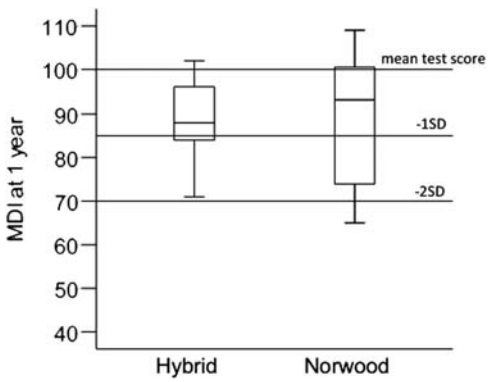

Figure 2: MDI at 1 year of age comparing hybrid and Norwood procedures. Boxplots showing MDI of the Bayley Scales of Infant Development II at 1 year of age in patients with HLHS and other UVH treated by the hybrid procedure ($n = 9$) and the Norwood procedure ($n = 11$), $P = 1.0$.

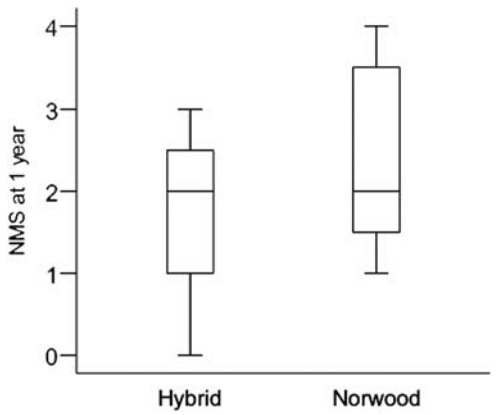

Figure 1: NMS at 1 year of age comparing hybrid and Norwood procedures. Boxplots showing NMS at 1 year of age in patients with HLHS and other UVH treated by the hybrid procedure ($n = 9$) and the Norwood procedure ($n = 11$), $P = 0.35$.

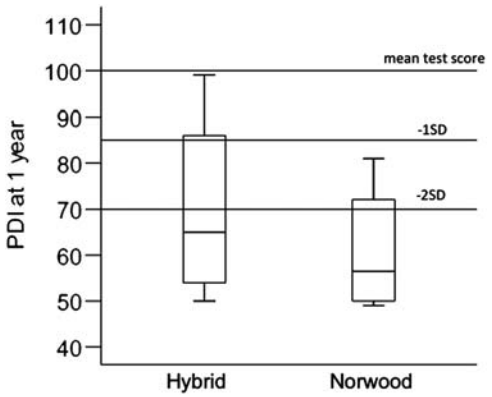

Figure 3: PDI at 1 year of age comparing hybrid and Norwood procedures. Boxplots showing PDI of the Bayley Scales of Infant Development II at 1 year of age in patients with HLHS and other UVH treated by the hybrid procedure ($n = 9$) and the Norwood procedure ($n = 11$), $P = 0.18$.

and perioperative parameters (Table 1) were not related to 1-year mortality.

Predictors of neurodevelopmental outcome at 1 year of age

The combined (after Norwood stage I and II and after hybrid and comprehensive stage I and II procedures, respectively) duration of mechanical ventilation ($P = 0.03$), the combined length of ICU stays ($P = 0.04$) as well as the combined LOHS ($P < 0.001$) correlated inversely with MDI at 1 year of age. Antegrade flow in the ascending aorta at birth was associated with a higher MDI ($P = 0.02$), but not with the PDI. The combined LOHS was inversely correlated with PDI ($P = 0.01$). Higher body weight at the second procedure ($P = 0.004$) and male sex ($P = 0.01$) were associated with higher PDI. There was a trend that a PDI below 70 was associated with a smaller head circumference at the time of 1-year follow-up ($P = 0.06$). The type (surgery or catheter intervention) and the overall number of reinterventions during the first year of life did not correlate with neurodevelopmental outcomes. All other perinatal and perioperative parameters (Table 1) were not associated with MDI and PDI, and no variable was associated with NMS.

DISCUSSION

HLHS and related forms of UVH have become surgically treatable with the Norwood procedure [12]. As an alternative treatment option, the hybrid approach has been developed and continuously optimized [7–9]. This procedure postpones cardiopulmonary bypass surgery beyond the critical neonatal period with the aim to reduce mortality and to improve neurodevelopmental outcome. However, to the best of our knowledge, there is no study comparing neurodevelopmental outcome between patients treated with the hybrid or Norwood procedure.

In our study, cognitive as well as motor outcome at 1 year of age was below the norm for all patients, and we did not find an effect of treatment strategy on outcome. Only motor outcome was somewhat poorer in children undergoing Norwood procedure compared with those undergoing hybrid procedure (PDI 56.5 vs. 65.0), but the difference was not significant. Independent of the treatment strategy, the rate of moderate impairments was higher for the motor (60% PDI <70) than for the cognitive outcome (10% MDI <70). This is consistent with other studies [13] and may be due in part to the neurological abnormalities such as generalized hypotonia [14] or due to the lack of motor development experience associated with prolonged hospital stay [15]. The median MDI of 91 in our population was in the normal range and confirms the results of Tabbutt *et al.* [16] (median MDI of 90) at 1 year of age in patients with HLHS undergoing Norwood-type staged palliation. In contrast, motor outcome in our patients was lower than that in the cohort of Tabbutt *et al.* [16] (median PDI 57 compared to 73). This difference may be explained by the inclusion of a less severely affected study population in their cohort. Further, the low PDI in our study may be due to the fact that the reference norms for the Bayley Scales of Infant Development are obtained from the USA and may be different in other populations. This is supported by a study performed in Australia where healthy term-born children had a mean PDI of 88.3 at 1 year of age instead of the reference norm of 100 [17].

Risk factors for adverse neurodevelopmental outcomes included postoperative factors such as duration of mechanical ventilation, duration of combined ICU stays and LOHS, predicting poorer cognitive outcome, whereas poorer motor outcome was predicted by the combined LOHS, female sex and lower weight at the second procedure. These results confirm those of previously published studies [18–20]. In our study, an antegrade aortic flow at birth was predictive of better cognitive outcomes. A similar association has been shown for school-aged children after Norwood procedure by Mahle *et al.* [18]. They showed that children with an aortic valve atresia demonstrated lower math achievement test scores after Norwood procedure or heart transplantation for HLHS.

We also examined the mortality of our cohort. Overall, 1-year mortality rate (36%) was high, but comparable to other populations treated with the Norwood procedure where it ranged between 31 and 48% [3, 21]. In our study, mortality rate after hybrid procedure (31%) was similar to that after Norwood procedure (39%), which confirms a recently published study by Pizarro *et al.* [22]. Predictors of mortality in our study included smaller size of the ascending aorta and lower birth weight, confirming findings of the past decade [21, 22].

Study limitations are the small study population in a single-centre setting without randomization of patients into treatment groups, potentially resulting in a bias of healthier patients treated with the hybrid procedure, although only the diameter of the ascending aorta was different between both groups before first surgical procedure (Table 1). Furthermore, perioperative intensive care management was not standardized, and cardiac variables such as myocardial function or degree of oxygen saturation were not systematically collected. Neuromonitoring prior to surgery at the time of study was limited to cerebral ultrasound and did not include routine cerebral magnetic imaging or cerebral function monitoring.

Based on the results of this study, it remains unclear whether the hybrid procedure can reduce mortality and neurological morbidity. Many aspects contribute to these two outcome parameters and need to be considered. Confounding factors include medical risk factors and anatomical conditions. For example, the larger diameter of the ascending aorta in the hybrid group may reflect the inclusion of infants with a better cerebral perfusion, existing already during intrauterine life, which per se might lead to a better cognitive outcome. Possible disadvantages of the hybrid procedure include the persistent abnormal cerebral blood flow and the need for more reinterventions such as re-dilatation of the pulmonary arteries. Furthermore, later age at surgery may be associated with a higher rate of acquired cerebral abnormalities [23]. Besides the anatomic factors and the modifiable clinical care strategies, there is also evidence of congenitally acquired brain injury in term newborns with CHD due to impaired early brain development already *in utero* as a result of abnormalities in cerebral blood flow [24]. Furthermore, it remains to be proved whether once the learning curve for the relatively new hybrid procedure has been completed, it might contribute to a better outcome.

Thus, it remains of outmost importance to determine the outcome of children treated with hybrid procedure in comparison to that of the Norwood procedure to establish the best treatment strategy for this most vulnerable population. This can only be achieved by performing a large multicentre randomized trial, in

which the effect size can be based on the results of our study and in which all potential risk factors such as preoperative delayed brain development and brain injury, intra- and postoperative factors and socio-demographic factors need to be considered.

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