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Impact of Whole-Body Perfusion in Postoperative Outcomes After Aortic Arch Reconstruction Surgery in Neonates and Infants

Rodrigo Sandoval Boburg, MD,[1] Charlotte Faust, MD,[2] Tobias Kruger, MD,[1] Migdat Mustafi, MD,[1] Harry Magunia, MD,[2] Felix Neunhoeffer, MD,[3] Michael Hofbeck, MD, PhD,[3] Christian Schlensak, MD, PhD[1]

[1]Department of Thoracic and Cardiovascular Surgery, University Hospital Tübingen, Eberhard-Karls-University Tübingen, Hoppe-Seyler-Str. 3, 72076 Tübingen, Germany; [2]Department of Anaesthesiology and Intensive Care Medicine, University Hospital Tübingen, Eberhard-Karls-University Tübingen, Hoppe-Seyler-Str. 3, 72076, Tübingen, Germany; [3]Department of Pediatric Cardiology and Intensive Medicine, University Hospital Tübingen, Eberhard-Karls-University Tübingen, Hoppe-Seyler-Str. 3, 72076 Tübingen, Germany

ABSTRACT

Introduction: The aim of this study was to determine whether whole-body perfusion (WBP) consisting of a combined antegrade cerebral perfusion (ACP) and lower body perfusion (LBP) improves the outcome after aortic arch reconstruction surgery in neonates compared with ACP.

Methods: Sixty-five consecutive patients under one year of age who underwent aortic arch reconstruction as the main procedure or as part of a more complex surgery from 2014-2020 in our center were included. The patients were separated into two groups, according to the perfusion strategy, either ACP (34 patients) as the control group or WBP (31 patients) as the intervention group. LBP was achieved through an arterial sheath in the femoral artery. Outcome parameters were postoperative renal, gastrointestinal, and neurological complications and 30-day mortality.

Results: The patients in the WBP group showed lower intraoperative lactate levels and close to normal early postoperative renal and hepatic enzymes and LDH at PICU admission compared with the patients in the ACP group. The number of patients suffering from postoperative neurological complications and multiorgan failure was lower in the WBP group.

Conclusion: In our experience, the combined use of ACP and LBP through the femoral artery showed an improvement, regarding postoperative neurologic complications in neonates and infants undergoing aortic arch surgery.

INTRODUCTION

The evolution of surgical techniques aims for the reduction of postoperative complications. Early aortic arch surgery was performed under deep hypothermic cardiocirculatory arrest (DHCA). This technique was then replaced using antegrade cerebral perfusion (ACP), which allowed for higher systemic temperatures and led to improved results [Raees 2017; Pigula 2000]. Subsequently, the focus turned to lower body perfusion (LBP) with the purpose of avoiding organ ischemia. This perfusion strategy improves organ protection and decreases postoperative visceral malfunction [Algra 2012; Fernandes 2012; Hammel 2013; Cesnjevar 2016].

Various approaches of LBP have been described, from inserting a cannula in the descending aorta while performing the anastomoses to a subdiaphragmatic cannulation or a cannulation through a left-sided thoracotomy [Hammel 2013; Cesnjevar 2016; Fernandez-Doblas 2018]. Recently, we described a novel technique in a small series of patients in which an arterial sheath, introduced via the femoral artery connected to an extra pump in the heart-lung machine, is utilized for the establishment of simultaneous ACP and LBP, also named whole-body perfusion (WBP), this strategy proved to be simple and safe (Boburg 2020).

There is a significant number of studies comparing renal or hepatic dysfunction in children following complex aortic arch surgery performed with different perfusion techniques, compared to patients who underwent the same surgery under DHCA evaluating just one or two organ systems [Raees 2017; Fernandes 2012; Cesnjevar 2016; Algra 2012; Hoxha 2018]. Data about a comparison between the currently established technique of ACP with a (WBP) technique using ACP and LBP are sparse. The objective of this study was to compare the intra- and postoperative values of renal and hepatic function as well as major postoperative complications and 30-day mortality between patients who underwent aortic arch reconstruction surgery just with ACP or WBP.

METHODS

Patient selection and grouping: We retrospectively screened all pediatric patients under one year of age, who underwent aortic arch surgery at the University Hospital Tübingen from January 2014 to July 2020. Patients were eligible for this study if they underwent surgeries, such as

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Correspondence: Dr. Rodrigo Sandoval Boburg, Department of Thoracic and Cardiovascular Surgery, University Hospital Tübingen, Hoppe-Seyler-St. 3, 72076 Tübingen, Germany, Telephone +49 (0) 7071 – 29 86638, Fax +49 (0) 7071 – 29 3298; email: rodrigo.sandoval2@gmail.com.

the Norwood procedure, Damus-Kaye-Stansel anastomoses, or an aortic arch reconstruction due to hypoplasia as a primary or a redo surgery. Figure 1 shows a patient selection chart. (Figure 1) All procedures were performed by the same surgeon. Before January 2017, all patients undergoing any of these procedures were treated with ACP and moderate hypothermia. After January 2017, a WBP technique was established at our center consisting of the standard ACP with LBP and mild hypothermia. All pediatric patients undergoing aortic arch surgery after this date were treated with WBP. After selection, there were 31 patients in the WBP group and 34 patients in the ACP group. All patients were treated by the same experienced surgeon and the same team of cardiac anesthesiologists throughout the study period.

Perfusion strategies: ACP was established through a polytetrafluoroethylene (PTFE) shunt anastomosed to the brachiocephalic trunk, where the arterial cannula was inserted. During ACP, perfusion was established at a rate of 50-80 ml/kg and monitored with near-infrared spectroscopy. Patients in this group were cooled down to 28°C during aortic arch repair; after the repair was finished and complete CPB was reinstated, patients were warmed up.

LBP has established through ultrasound-guided percutaneous cannulation of the femoral artery with a 3 Fr. or 4 Fr. arterial sheath; this was performed after anesthesia induction by experienced cardiac anesthesiologists. This procedure previously had been described by our group [Boburg 2020]. The arterial sheath was connected to the cardiopulmonary bypass (CPB) through an independent pump. During aortic clamping and aortic arch reconstruction, combined ACP and LBP were established and the flowrate of LBP was 20-40ml/kg. This was measured with a Fumaflow Flowsensor (Fumedica, Muri, Switzerland) and adjusted, depending on blood pressure (mean arterial pressure > 40mmHg), lactate levels (<3mmol/L), and peripheral oxygen saturation (>90%). Patients in this group were cooled down to a target temperature of 30°C. After aortic arch reconstruction was completed, full-body perfusion was established.

After surgery and transfer to the pediatric intensive care unit (PICU), the arterial sheath was removed as quickly as possible to avoid any malperfusion or other limb ischemia.

Parameter analysis: Anthropometric parameters included gender, age, height, and weight.

Intraoperative parameters, such as maximum lactate level at reperfusion, duration of cardiopulmonary bypass (CPB), and aortic cross-clamping time, were recorded.

Creatinine levels and hepatic parameters, including alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), lactate dehydrogenase (LDH), and international standardized ratio (INR), were recorded preoperatively, after transfer to the PICU, 24h and 72h postoperatively.

At the PICU, examination of the lower extremities was performed on a regular basis, at least once every 8 hours, looking for any signs of malperfusion or limb ischemia after sheath removal.

Length of stay (LOS) at the PICU and duration of mechanical ventilation also were recorded.

Primary outcome: The main objective was to compare major early postoperative complications. These included major renal, neurologic, and gastrointestinal complications. Major renal complications were defined as the requirement of renal replacement therapy (RRT). The decision to start RRT was made based on current guidelines [Khwaja 2012]. Major neurologic complications included the appearance of neurologic symptoms like seizures and intracranial bleeding or ischemia; patients underwent transcranial ultrasound examination for any major congenital malformations before surgery. After surgery, transcranial ultrasound was performed twice a week in all patients; in patients with ECLS, ultrasound was performed daily to check for any bleeding. Major gastrointestinal complications were defined as any impairment of the gastrointestinal system that developed postoperatively requiring treatment and prolonging the LOS in the PICU. Multiorgan failure (MOF) was defined as dysfunction of two or more organ systems defined by clinical and biochemical parameters.

Thirty-day mortality was recorded and compared between both groups.

Statistical analysis: Statistical analyses were performed using the SSPS 23.0 (IBM Corporation, Armonk, NY, USA) software. Normal distribution was checked using the Kolmogorov-Smirnov test. Continuous variables are reported as means and standard deviation if they fulfilled criteria of a normal distribution, otherwise median and interquartile ranges are reported. Normally distributed variables were compared using the Student t-test and not normally distributed variables were compared using the Mann-Whitney U-test. Ordinal variables are reported as absolute values and percentages and were compared with the X^2-test.

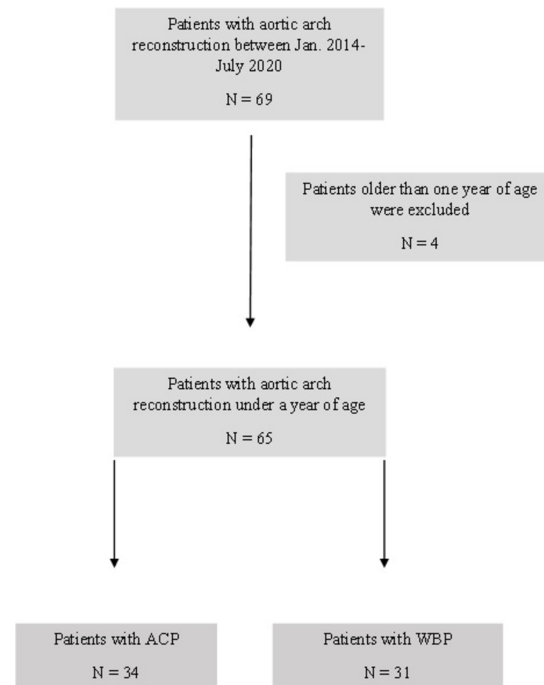

Figure 1.

Table 1. Baseline values

	Whole-body perfusion	Antegrade cerebral perfusion	*P*-value
Gender (m)	19 (61%)	23 (63.9%)	0.5
Age (days)	14 (9-46)	12 (7.25-27)	0.04
Weight (kg)	3.8 ± 1.52	3.5 ± 0.8	0.8
Preoperative parameters			
Creatinine (mg/dl)	0.6 ± 0.4	0.6 ± 0.3	0.7
ASAT (U/l)	39 (29-56)	34 (28-48)	0.5
ALAT (U/l)	18 (12-34)	18.5 (11.5-37.2)	0.9
LDH (U/l)	357 (287-444)	361 (268-452)	1
INR	1.2 ± 0.2	1.1 ± 0.2	0.03
Surgeries			
Norwood	18 (58%)	19 (54.3%)	1
Aortic arch reconstruction	7 (22.5%)	12 (34.3%)	0.8
Damus-Kaye-Stansel and aortic arch	2 (6.5%)	2 (5.7%)	1
Arterial switch and aortic arch	4 (12.9%)	1 (2.9%)	0.5
VSD, Truncus arteriosus communis and aortic arch reconstruction	0	2 (2.9%)	0.8

Preoperative anthropometric, renal, and hepatic parameters and types of surgery performed. ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; INR, international standardized ratio; LDH, lactate dehydrogenase; VSD, ventricular septal defect

Table 2. Between group comparison of intraoperative course

	Whole-body perfusion	Antegrade cerebral perfusion	*P*-value
Cardiopulmonary bypass (min)	165.1 (115.5-220.5)	166.6 (122.8-206)	0.3
Cross-clamp (min)	71.5 (61.25– 116)	78 (58.5 – 93)	0.8
Max lactate at reperfusion (mmol/L)	2.6 ± 1.3	4.1 ± 1.7	0.01
RBC Transfusion (ml)	400 (307 – 900)	600 (300-750)	0.7
FFP Transfusion (ml)	300 (280-399)	600 (300 - 600)	0.03

Intraoperative parameters. FFP, fresh frozen plasma; RBC, red blood cells

We reported our data, according to the STROBE guidelines [Von Elm 2007]. Statistical analysis was performed in accordance with the guidelines of our association [Hickey 2015].

The ethics commission board approved the study (project number 461/2019BO2). Due to the retrospective nature of the study, written consent was waived.

RESULTS

Aside from age, there were no significant differences, regarding anthropometric data between groups. Mean age in the ACP group was significantly younger when compared with the WBP group. This is due to one patient having a re-do surgery 6 months after the initial Norwood surgery; a second patient had a pulmonary banding as a first operation and a Norwood-type surgery about 4 months later; and a third patient had a late diagnosis and was referred to our center when he was 8 months old.

Regarding preoperative renal and hepatic parameters, we found a minimal difference in the INR. This difference had no influence in the type and timing of treatment. Surgeries performed are displayed in Table 1. (Table 1)

Table 2 shows the intraoperative parameters in both groups. (Table 2)

The different perfusion techniques had no effect on the length of surgery, and there was no difference in CPB time or aortic cross-clamp time between the groups. Notably, the installation of LBP did not extend the procedure, with respect to time or invasiveness. Importantly, patients treated with WBP had significantly lower lactate levels during reperfusion when compared with the ACP group.

Table 2 also displays the need for blood product transfusions in both groups. It is important to note that the red blood cells (RBC) and fresh frozen plasma (FFP) transfusions were recorded as units but not as exact milliliters. The amount of transfused RBC did not differ between groups. The amount of FFP transfused, however, was significantly lower in the WBP group.

We compared the number of patients transferred to the PICU with an open thorax, due to the development of myocardial oedema, being at high risk for pericardial tamponade due to ongoing bleeding or the need for veno-arterial extracorporeal membrane oxygenation (VA-ECMO) implantation due to severe hemodynamic impairment. There were 22 (61%) patients in the ACP group and 18 (58%) in the WBP group who were transferred with an open thorax to the PICU.

In the next step, we analyzed the postoperative clinical and biochemical parameters. The results are shown in Table 3.

There was no difference regarding LOS and duration of mechanical ventilation between groups. At the time of arrival to the PICU, data show that the liver enzymes ALAT and ASAT were significantly higher in the ACP group. Similarly, the LDH on average was higher in the ACP group ($P < 0.001$). Twenty-four hours after PICU admission, the liver enzymes showed a decrease toward normal values in the ACP group, and there was a small but significant difference in INR and lactate levels, with the WBP group having higher values. The values stayed constant throughout the following 48 hours and showed no difference in any of the parameters measured.

The patients in the WBP group were regularly examined for hematomas, signs of malperfusion or limb ischemia in the PICU. Notably, we did not record any complications directly associated with transfemoral LBP, particularly no bleeding in the groin, retroperitoneal, or vascular problems.

The postoperative complications data show that the absolute number of complications was greater in the ACP group than in the WBP group. There were five (14.7%) patients in the ACP and three (9.7%) in the WBP groups who needed postoperative RRT. This difference proved to be insignificant between the groups and shows a low kidney affection rate in these procedures.

The only major gastrointestinal complication we recorded in this cohort was NEC. There were four (11.8%) and three (9.7%) cases in the ACP and WBP groups, respectively.

There were two cases of MOF (5.9%) in the ACP group, both leading to death. On the contrary, in the WBP group, there was one case of MOF. This patient died due to complications of MOF.

Interestingly, the incidence of neurological complications differed between groups. There were two patients in the ACP group who developed seizures and four patients who suffered from intracranial bleeding. There were no recorded neurological complications in the WBP group leading to a statistical significance regarding this parameter ($P = 0.02$).

Mortality was not significantly different between the groups. There were three (9.7%) patients in the WBP group who died within 30 days after surgery. One patient died from complications of MOF and repeated lung bleeding, and another patient died due to massive aspiration and hypoxic brain damage over two weeks after surgery. A third patient died from complications of heart insufficiency. In the control group, there were two (5.9%) patients who died as a consequence of MOF.

DISCUSSION

In recent years, attention has turned to the investigation of the impact of WBP on postoperative morbidity and mortality after aortic arch reconstruction in neonates and infants. Among the advantages of using a WBP is the possibility of using less profound hypothermia as opposed to DHCA or ACP due to the lack of splanchnic isquemia [Raees 2017]. In this series, we did not operate under DHCA, and in the ACP patients we used moderate hypothermia for visceral protection, nevertheless, the target temperature was lower than compared with WBP, which is consistent with current literature [Raees 2017; Hammel 2013; Fernandez-Doblas 2018]. The reduced need for FFP transfusions in the WBP group may be interpreted as an effect of the higher intraoperative temperatures and continuous liver perfusion, which may translate in less distortion of the coagulation system, although to prove this, an analysis of intraoperative transfusions and coagulation factor substitution should be performed. The fact that there was no difference in CPB or the aortic cross-clamping time between the groups was probably because LBP has no effect on the surgical correction and workflow itself because of preoperative cannulation of the femoral vessels. After induction of anesthesia, the cardiac anesthesiologists cannulated ultrasound controlled the femoral artery, thus minimizing invasiveness during surgery; this procedure showed no postoperative complications.

The maximum lactate levels at reperfusion were significantly lower in the WBP group, probably as a consequence of uninterrupted visceral perfusion with LBP. Interestingly, after 24 hours in the PICU, the WBP group showed a slight but significant increase in lactate levels compared with the ACP group. This increase may be multifactorial and probably does not correlate to the perfusion strategy during surgery. For the rest of the time recorded, the lactate levels returned to normal.

The WBP group showed significantly lower hepatic enzyme levels and LDH at PICU arrival, a finding that corroborates the difference in hepatic perfusion. Interestingly, after 24 hours, the hepatic values of the patients in the control group decreased to normal values and a difference between the groups no longer existed. This finding was surprising because in our cohort, it was evident that even after a period of relative ischemia, the liver regained normal function in most patients after 24 hours. There have been groups, who found an improvement in INR and prothrombin time in patients with a combined cerebral and splanchnic perfusion compared with patients with ACP [Fernandez-Doblas 2018]. In our cohort, there was a slight increase in INR in the WBP group after 24 hours. This showed no significant relevance and at 72 hours and did not translate to increased postoperative bleeding.

The renal function defined by creatinine values didn't

Table 3. Between group comparisons of PICU course

	Whole-body perfusion	Antegrade cerebral perfusion	*P*-value
LOS at the PICU (d)	13 (9 – 40)	15 (9 – 27.5)	0.9
Mechanical Ventilation (d)	10.3 ± 9.2	11.3 ± 9.1	0.4
Arrival to the PICU			
ASAT (U/l)	69 (44 – 110)	85 (61 – 139)	0.1
ALAT (U/l)	11 (9 - 19)	21 (16 – 28)	<0.01
INR	1.1 ± 0.1	1.1 ± 0.1	0.2
LDH (U/l)	387 (332 – 477)	445 (363 – 556)	0.1
24 hours postoperative			
Creatinine (mg/dl)	0.5 ± 0.2	0.6 ± 0.3	0.3
ASAT (U/l)	75 (43 – 119)	50 (38 – 139)	0.3
ALAT (U/l)	12 (8 – 18)	14 (9 – 24)	0.4
INR	1.3 ± 0.1	1.2 ± 0.1	<0.01
LDH (U/l)	406 (293 – 643)	374.5 (316 – 633)	0.8
Lactate (mmol/L)	2.5 ± 2.2	1.7 ± 0.9	0.01
72 hours postoperative			
Creatinine (mg/dl)	0.6 ± 0.2	0.6 ± 0.3	0.5
ASAT (U/l)	32 (20 - 57)	26 (18 – 44)	0.4
ALAT (U/l)	9 (7 - 17)	9 (5 – 15)	0.5
INR	1.2 ± 0.2	1.1 ± 0.2	0.5
LDH(U/l)	331 (227 – 609)	333 (269 – 473)	1
Lactate (mmol/L)	1.3 ± 0.6	1.4 ± 0.5	0.5

Postoperative renal and hepatic parameters and lactate levels. ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; INR, international standardized ration; LDH, lactate dehydrogenase; LOS, length of stay; PICU, pediatric intensive care unit

Table 4. Short-term outcome and 30-day mortality

	Whole-body perfusion	Antegrade cerebral perfusion	*P*-value
RRT	3 (9.7%)	5 (14.7%)	0.7
Multiorgan failure	1 (3.2%)	2 (6%)	1
NEC	3 (9.7%)	4 (11.8%)	1
Neurological complications	0	6 (17.6%)	0.02
30-day mortality	3 (9.7%)	2 (6%)	0.6

Major postoperative complications. NEC, necrotizing enterocolitis; RRT, renal replacement therapy

differ between groups. This finding contrasts with results of other groups, who showed an improved renal function and glomerular filtration rate in patients treated with lower body perfusion [Raees 2017; Hammel 2013]. However, if there was an improved visceral protection, it did not translate into shorter ICU times: There was no difference in the length of mechanical ventilation or length of stay at the ICU between both groups, this also was consistent with other groups' results [Raees 2017].

A rationale for instating LBP would be improved visceral perfusion, hence, protection. Under mild hypothermic conditions, LBP via a transfemoral sheath should be capable of meeting the organs' oxygen and metabolic demands in neonates and infants, thus prolonging the time characterized as safe for aortic arch surgery. As seen in Table 4, the WBP group had fewer complications in most categories. (Table

4) The only major gastrointestinal complication, which was seen in this cohort, was NEC. There was no significant difference in the incidence between the groups. These results show that some organs are more vulnerable than others to transient ischemia and, according to our data, the gut seems to suffer more than the liver and kidneys. There were two patients in the ACP group and one in the group who suffered from MOF in the early postoperative period. The only patient in the WBP group and two in the ACP group died as a consequence of this complication.

Unlike visceral complications, neurological complications showed a significant difference between the groups. It was the category where most complications occurred in the ACP group. At first glance, there is no striking and plausible explanation for improved neuroprotection due to the use of LBP. The difference in the number of neurological complications may imply a better cerebral perfusion in the WBP group. As ACP was being researched, there was evidence that it provided a certain protection of kidney and splanchnic organs, when compared with DHCA. It is through collaterals that some perfusion of the lower body is achieved through ACP [Pigula 2000; Algra 2012; Cesnjevar 2016]. With combined upper and lower body perfusion, the necessity of collateral vessel perfusion of the lower body is eliminated, which may even further improve cerebral perfusion by reducing the steal phenomenon caused by a lack of perfusion in the left side of the brain and lower body that ensues during ACP, thus causing fewer postoperative complications. To gain further insights and confirm this hypothesis, a study needs to be made in which cerebral blood flow and oxygen saturation are measured during ACP versus WBP.

Other aspects of lower body perfusion, which may lead to a better neurological outcome, are improved spinal cord protection and less metabolic distortion during reperfusion and re-warming. However, we cannot fully explain our observation of significantly less neurological complications in the WBP group and additional investigations are needed.

The 30-day mortality did not show any significant difference between groups as the event rate was low.

Due to the low incidence of this condition, it is difficult to recruit enough patients to reach significant results in a single center approach. Nevertheless, there is a trend in favor of WBP regarding postoperative complications. Different groups have described various cannulating sites to achieve a descending aortic perfusion during aortic arch reconstruction, including a direct cannulation of the descending aorta through a left sided thoracotomy or a cannulation of the umbilical artery [Fernandez-Doblas 2018; Rajagopal 2010]. We proposed a cannulation technique as described earlier with an arterial sheath introduced into the femoral artery, connected to an extra pump in the heart lung machine, and delivering a perfusion of 20-40 ml/kg for the duration of the aortic arch repair [Boburg 2020]. It is important to note that in order to avoid any complications, as we have done so far, the arterial sheath should stay as short as possible in place.

Limitations: The results of this study are limited by the small sample size, its retrospective nature, and relatively long study period. Aortic arch hypoplasia is a rare disease, and this makes it difficult to achieve a large sample size. In order to extensively study this approach, a prospective multi-center study should be performed.

NIRS Data was used, but not recorded for every patient, which is why we can't report and analyze it.

The femoral artery, where the sheath was implanted, was not serially examined with ultrasound to check for partial clotting or obstruction, the examination was performed clinically in the PICU.

CONCLUSION

The results in this study were able to reproduce some of the previously published results. We showed that the combination of ACP and LBP through the femoral artery is a safe, feasible and reproducible procedure, which has the potential to reduce the postoperative complications in neonates and infants undergoing aortic arch reconstruction, especially neurological ones. Regarding long-term organ function and 30-day mortality, although we didn't find a significant difference, our results show a trend toward a lower number and severity of postoperative neurological complications with WBP.

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