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ORIGINAL ARTICLE

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Equal cerebral perfusion during extended aortic coarctation repair

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Key question

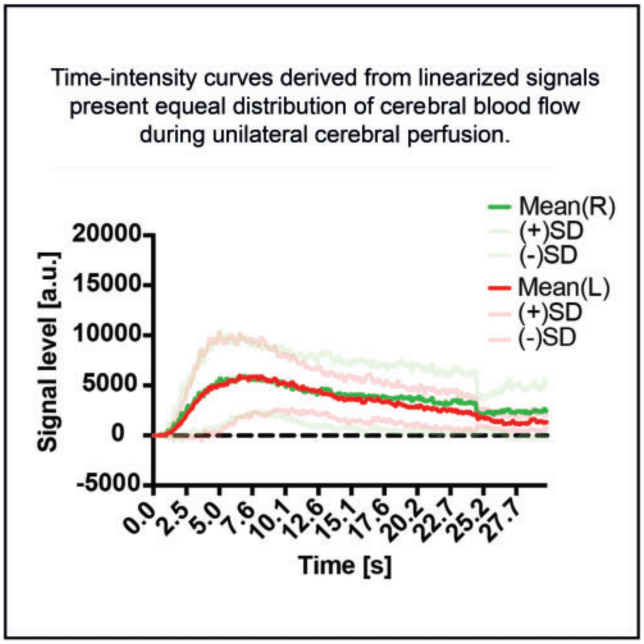
Is cerebral blood flow distribution comparable between hemispheres during unilateral cerebral perfusion?

Key finding(s)

T-CEUS confirmed homogeneous cerebral blood flow in both hemispheres during extended aortic coarctation repair.

Take-home message

Using T-CEUS, sufficient cerebral blood flow during unilateral cerebral perfusion via the innominate artery could be confirmed.



Abstract

OBJECTIVES: Aortic coarctation with distal aortic arch hypoplasia can be effectively addressed by coarctation resection with extended end-to-end-anastomosis (REEEA). Particularly, when unilateral cerebral perfusion (UCP) is established by clamping of left-sided supra-aortic vessels, the extent of cerebral blood flow distribution during repair remains undetermined, so far. Transfontanellar contrast-enhanced ultrasound (T-CEUS) can be utilized for real-time visualization and quantitative evaluation of cerebral blood flow. This study quantitatively evaluates cerebral perfusion during REEEA by using intraoperative T-CEUS.

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†The first two authors contributed equally to this study.

METHODS: In a prospective study, 9 infants with open fontanelle undergoing REEEA [median age: 13 days (range 1–34) and median weight 3.1 kg (range 2.2–4.4)] were intraoperatively examined with T-CEUS at 3 consecutive time-points: before skin incision, during UCP and after skin suture. A software-based analysis of 11 parameters was used for data evaluation. Absolute and relative blood flow in contralateral hemispheres was measured in side-by-side comparison, and referenced to baseline measurements.

RESULTS: No side-depend absolute or relative cerebral perfusion differences were found during REEEA, except for an increased relative 'wash-out-rate' ($P = 0.0013$) in favour of the right hemisphere after surgery. Compared to ipsilateral baseline levels, 'rise time' was transiently increased in right ($P = 0.0277$) and 'time-to-peak' in both hemispheres (right: $P = 0.0403$ and left: $P = 0.0286$), all during UCP.

CONCLUSIONS: The use of T-CEUS provided evidence for homogenous distribution of contrast agent in both hemispheres during UCP. T-CEUS can be utilized for the postprocedural evaluation of cerebral perfusion during congenital cardiac surgery.

Clinical Trial Registration: URL: http://www.clinicaltrials.gov Unique, Identifier: NCT03215628.

Keywords: Aortic coarctation • Extended end-to-end-anastomosis • Cerebral perfusion

ABBREVIATIONS

CPB	Cardiopulmonary bypass
NIRS	Near-infrared spectroscopy
POST	Postoperative
PRAE	Preoperative
REEEA	Coarctation resection with extended end-to-end-anastomosis
T-CEUS	Transfontanellar contrast-enhanced ultrasound
UCP	Unilateral cerebral perfusion

INTRODUCTION

Cerebral perfusion of infants with congenital heart defects is a critical determinant of successful cardiac surgery. Assuming a symmetrical anatomy of the cerebral arteries, a single vessel (innominate artery) can supply both cerebral hemispheres by the circle of Willis. This principle is crucial for using unilateral cerebral perfusion (UCP) via the innominate artery during repair of aortic arch anomalies [1–3].

By using the coarctation resection with extended end-to-end-anastomosis (REEEA) technique from the lateral approach, all left-sided supra-aortic vessels are clamped, hence leaving UCP for neuroprotection [4–7]. Despite outcome seems encouraging over decades of clinical experience, neonates who require isolated coarctation or complete aortic arch repair may be at significant risk of neuro-developmental delay [8]. Although an intrinsic cause is suggested, to date and our knowledge, no intraoperative measurements with quantification of cerebral blood flow during REEEA are available, leaving an uncertainty regarding safety by using this technique.

Brain structures and cerebral vasculature including their communicating arteries can be imaged by ultrasound in neonates during aortic arch repair [1–3]. Combined intraoperative transfontanellar/transtemporal 2- and 3-dimensional colour and pulse-wave Doppler has been implemented by our group previously to display the intensity of vessel perfusion in both hemispheres during UCP [3]. The additional use of intravenous ultrasound contrast agents also opens up the possibility of capturing the smallest vessels and tissue perfusion itself. The resulting information gives a much more precise insight into brain perfusion than conventional Doppler procedures [9–11]. Transfontanellar contrast-enhanced ultrasound (T-CEUS) can be used for real-time visualization and secondary software quantification of contrast agent dynamics allowing detailed mapping of cerebral blood flow [12, 13].

The aim of this study was to verify by T-CEUS whether cerebral blood flow distribution during REEEA is symmetrical.

MATERIALS AND METHODS

Study design

The study is part of a prospective monocentric, explorative trial evaluating cerebral blood flow during congenital cardiac surgery by using T-CEUS, presenting a subgroup analysis of patients undergoing REEEA (URL: http://www.clinicaltrials.gov. Unique identifier: NCT03215628). Intraoperative T-CEUS was performed by a single ultrasonography specialist [Deutsche Gesellschaft für Ultraschall in der Medizin (DEGUM), level III] [13]. All examinations and procedures were performed at the University Hospital Erlangen, Germany, between November 2017 and December 2020.

Ethical statement

The local ethics committee approved the full trial protocol (20_17B). Before inclusion, informed consent for the study and to the off-label use of the ultrasound contrast agent was obtained from all parents or legal guardians.

Patients

Inclusion criteria were term infants with open fontanelle undergoing UCP from a lateral approach without the use of cardiopulmonary bypass (CPB), and availability of the entire scientific team composed of a surgeon, a solitary ultrasonography specialist and documental assistant. Patients with haemodynamic instability or critical illness, as well as an insufficient opening of the fontanelle, were gauged as non-eligible for examination. In all patients, a communicating circle of Willis was documented by ultrasound prior surgery [3].

Surgery

The technical aspects of REEEA have been extensively described in the past [4–7]. REEEA or end-to-side repair in case of arch

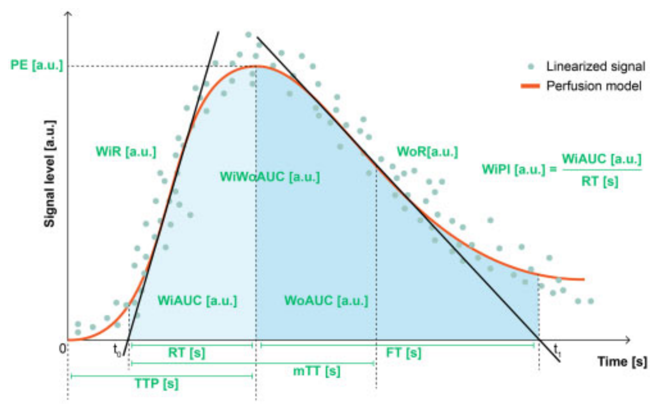

Figure 1: Quantitative parameters of transfontanellar contrast-enhanced ultrasound. Schematic diagram of all analysed transfontanellar contrast-enhanced ultrasound parameters derived from linearized signals (grey dots) by applying a bolus perfusion model (red line). Time–intensity curve: FT: fall time; mTT: mean-transit-time; PE: peak enhancement; RT: rise time; TTP: time to peak; WiAUC: wash-in-area-under-the-curve; WiPI: wash-in perfusion index; WiR: wash-in rate; WiWoAUC: wash-in-wash-out-area-under-the-curve; WoAUC: wash-out-area-under-the-curve; WoR: wash-out rate.

Video 1: Preoperative TCEUS measurement.

interruption were performed via left postero-lateral thoracotomy in the third intercostal space by using the muscle-sparing technique. When possible, the parietal pleura was kept closed [14]. Aortic cross-clamping implied that neuroprotection was warranted by UCP, when the proximal aortic arch and descending aorta were clamped together with the left-sided supra-aortic vessels. Extended end-to-end or end-to-side anastomosis was performed by a running 7–0 Polypropylene (Prolene®, Ethicon GmbH, Norderstedt, Germany) suture in all cases. Patient's core body temperature was maintained at 32–34°C using a Bair Hugger™ temperature monitoring system (3M Deutschland GmbH, Neuss, Germany) until antegrade aortic flow was released. No perioperative anticoagulation was used.

Time-points

All measurements were performed during 3 consecutive time-points:

(i) before skin incision (PRAE), (ii) during UCP and (iii) after skin suture (POST).

Transfontanellar contrast-enhanced ultrasound

Technical aspects of T-CEUS for monitoring brain perfusion during neonatal heart surgery have been described by our group [13]. For all analyses, both hemispheres (right/left) and the superior sagittal sinus (venous) were outlined. The software generated 11 dynamic flow parameters, which were used for subsequent analyses (Fig. 1 and Table 1).

A regions of interests was defined over each hemisphere measuring $\sim$13.0 ± 0.02 cm^2 and over the sagittal sinus measuring 0.2 ± 0.02 cm^2. Derived quantitative information about intracerebral flow characteristics was depicted in various flow parameters via colour-coded maps.

While performing T-CEUS, it was kept caution that no actions could interfere with the measurements, such as electrocauteries, and that the surgical setting remained unaffected. Since the other parameters such as temperature or circulation were not changed during the clamping phase, the time of contrast agent injection was not precisely defined in this phase (Video 1).

Haemodynamic measurements

At all time-points, heart rate, mean arterial blood pressure measured in the right radial artery, central venous pressure and near-infrared spectroscopy (NIRS) were recorded. Measurement of regional saturation was performed by continuous plotting of the somatic reflectance oximetry in both frontal hemispheres, and at the renal area (INVOS; Medtronic, Minneapolis, MN, USA).

Statistical analysis

Parameters are given as mean values with standard deviation or median with ranges. Cerebral blood flow parameters of T-CEUS were compared to contralateral hemispheres (left vs right) for each time-point. To evaluate changes of cerebral blood flow with respect to hemispheres throughout surgery, absolute values of each flow parameter were compared to its ipsilateral baseline (PRAE) measurements. To correct for the high inter-individual absolute variances, relative proportions (%) of each parameter to its contralateral hemisphere were compared for each time-point. Hence, relative T-CEUS parameters were calculated as follows:

$$\%\text{Proportion right hemisphere} = \frac{\text{TCEUS parameter}_{\text{right}}}{\text{TCEUS parameter}_{\text{right}} + \text{TCEUS parameter}_{\text{left}}}\,[\%].$$

Data were analysed by mixed-effects model in case of missing values or two-way Analysis of variance (ANOVA) followed by Dunnett's (absolute values) Sidaks's (relative values) test for multiple comparisons. The statistical evaluation is carried out using GraphPad Prism 9 (GraphPad Software, Inc., La Jolla, CA, USA). With a two-sided *P*-value of ≤0.05, the values can be regarded as statistically significant.

RESULTS

In all examined patients, an open circle of Willis was attested by ultrasound. A total of 9 patients (n = 4 males), 8 with aortic coarctation and 1 with interrupted aortic arch (Type A), were included in the analysis. The median age and weight were 13 days (range 1–34) and 3.1 kg (range 2.2–4.4), respectively.

Using T-CEUS, it was feasible to depict cerebral vasculature and perfusion in different anatomical regions. While the

Table 1: Description of T-CEUS flow parameters

Parameter	Abbreviation	Unit	Explanation
Peak enhancement	PE	Arbitrary units (a.u)	Maximum signal intensity
Wash-in-area-under-the-curve	WiAUC	Arbitrary units (a.u)	Integral from start (t_0) to peak
Rise time	RT	Seconds (s)	Time from t_0 to peak
Mean-transit-time	mTT	Seconds (s)	Ratio of volume and flow
Time-to-peak	TTP	Seconds (s)	Time to maximum signal
Wash-in rate	WiR	Arbitrary units (a.u)	Maximum slope
Wash-in perfusion index	WiPI	Arbitrary units (a.u)	WiAUC/RT
Wash-out-area-under-the-curve	WoAUC	Arbitrary units (a.u)	Integral from peak to loss of signal (t_1)
Wash-in-wash-out-area-under-the-curve	WiWoAUC	Arbitrary units (a.u)	WiAUC + WoAUC
Fall time	FT	Seconds (s)	t_1 - TTP
Wash-out rate	WoR	Arbitrary units (a.u)	Minimum slope

T-CEUS: transfontanellar contrast-enhanced ultrasound.

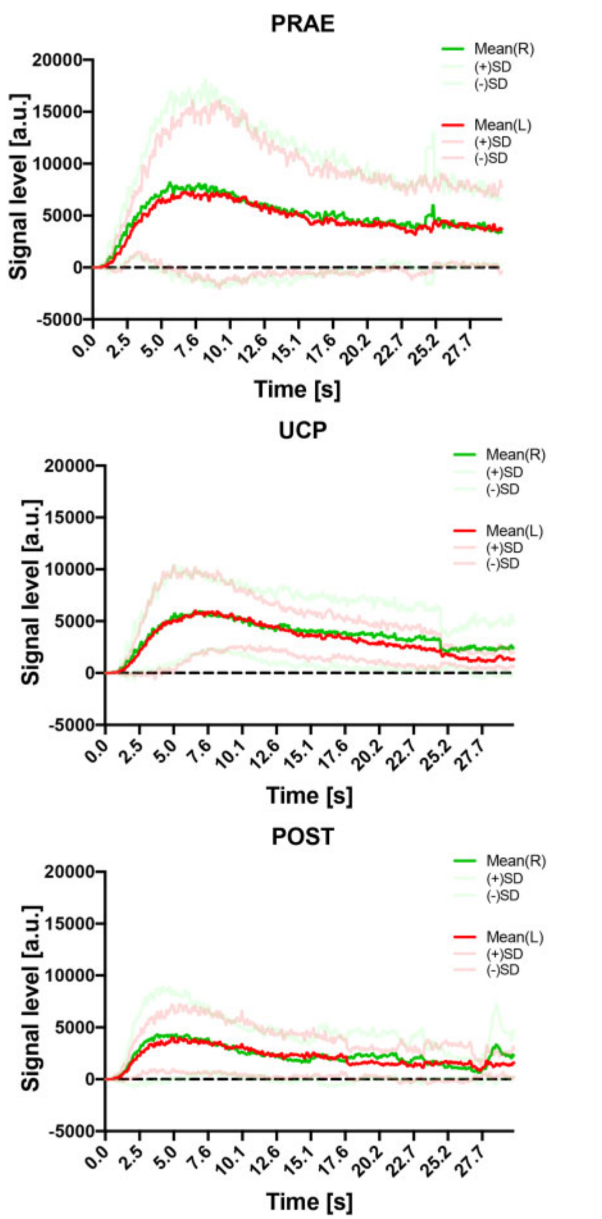

Figure 2: Time–intensity curves derived from linearized signals of the right (R, green) and left (L, red) hemisphere. Light colours represent +1 SD and -1 SD. POST: after skin closure; PRAE: before skin incision; SD: standard deviation; UCP: unilateral cerebral perfusion.

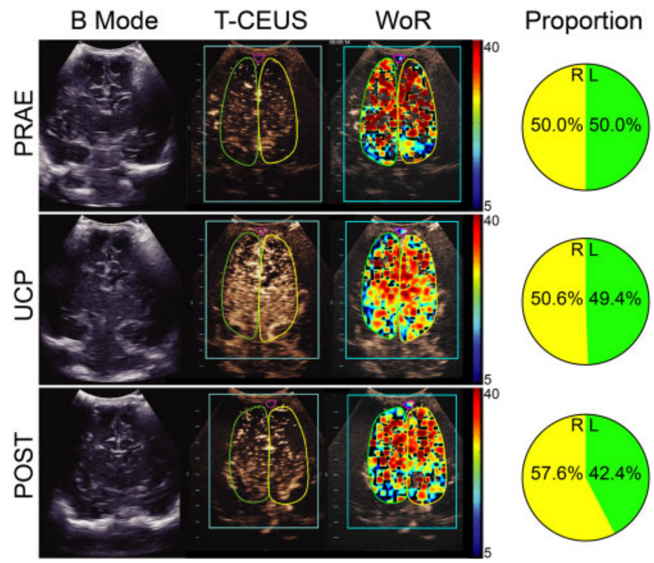

Figure 3: Quantification and analysis of T-CEUS parameters. From left to right: B Mode ultrasound (B Mode) for anatomical identification, contrast-enhanced ultrasound of microbubble signals, WoR as quantified colour-coded parameter, and proportion of signal distribution for each hemisphere. Note the homogenous distribution of T-CEUS signal during preoperative and UCP in contrast to postoperative state. POST: after skin closure; PRAE: before skin incision; T-CEUS: transfontanellar contrast-enhanced ultrasound; UCP: unilateral cerebral perfusion; WoR: wash-out-rate.

hemispheres showed immediate arterial enhancement of contrast agent after injection, the superior sagittal sinus displayed the time-delayed venous return.

The total duration from first to last measurement was 94 ± 16 min. The mean interval between consecutive injections at different surgical stages was 55 ± 34 min. No side effects of the ultrasound contrast agent were documented during application.

Quantification of transfontanellar contrast-enhanced ultrasound parameters

The generated time–intensity curves showed no significant differences between hemispheres at each time-point (Fig. 2).

When compared to the contralateral hemisphere at each time-point, no side-dependent differences of T-CEUS

Table 2: Absolute T-CEUS parameters

Parameter	PRAE	UCP	*P*-value (UCP vs PRAE)	POST	*P*-value (POST vs PRAE)
PE (a.u.)					
V	22 452 ± 27 812	17 621 ± 24 223	0.92	23 999 ± 27 603	0.99
R	10 057 ± 8989	6864 ± 4286	0.58	4953 ± 4504	0.32
L	8171 ± 9120	6996.8 ± 4496	0.75	3661 ± 3065	0.31
P-value (R vs L)	0.88	0.97		0.90	0.88
WiAUC (a.u.)					
V	122 139 ± 149 278	96 098 ± 151 991	0.94	102 015 ± 103 909	0.95
R	36 982 ± 41 498	35 889 ± 32 623	0.99	14 952 ± 14 885	0.28
L	27 821 ± 37 336	24 154 ± 9049	0.86	9547 ± 7874	0.26
P-value (R vs L)	0.97	0.70		>0.99	
RT (s)					
V	7 ± 5	10 ± 4	0.97	7 ± 3	<0.05
R	5 ± 3	9 ± 6	0.03	5 ± 2	0.87
L	5 ± 2	6 ± 2	0.06	5 ± 2	0.87
P-value (R vs L)	0.81	0.76		0.89	
mTT (s)					
V	35 ± 16	44 ± 30	0.60	31 ± 12	0.84
R	26 ± 17	78 ± 63	0.06	36 ± 31	0.68
L	58 ± 53	43 ± 39	0.62	401 ± 37	0.61
P-value (R vs L)	0.07	0.51		0.68	
TTP (s)					
V	18 ± 9	20 ± 10	0.50	18 ± 6	0.99
R	6 ± 3	12 ± 8	0.04	6 ± 3	0.85
L	6 ± 2	8 ± 2	0.03	6 ± 2	0.71
P-value (R vs L)	0.87	0.69		0.96	
WiR (a.u.)					
V	4026 ± 5777	2908 ± 3489	0.84	4978 ± 6505	0.95
R	3528 ± 2468	2008 ± 1814	0.18	2044 ± 2232	0.28
L	2849 ± 2589	2205 ± 2002	0.45	1586 ± 1315	0.34
P-value (R vs L)	0.18	0.45		0.84	
WiPI (a.u.)					
V	13 933 ± 17 258	11 002 ± 15 144	0.93	14 776 ± 16 958	0.99
R	6625 ± 5932	4615 ± 2849	0.61	3262 ± 2956	0.32
L	5382 ± 5948	4590 ± 2890	0.75	2415 ± 2032	0.31
P-value (R vs L)	0.88	0.95		0.92	
WoAUC (a.u.)					
V	188 740 ± 234 088	198 334 ± 309 316	>0.99	145 279 ± 146 466	0.90
R	92 378 ± 105 754	44 989 ± 19 176	0.59	39 155 ± 38 826	0.38
L	77 226 ± 97 795	59 158 ± 16 852	0.54	25 765 ± 21 320	0.34
P-value (R vs L)	>0.99	0.61		>0.99	
WiWoAUC(a.u.)					
V	310 879 ± 383 283	307 529 ± 468 308	>0.99	247 294 ± 250 357	0.92
R	129 359 ± 147 234	64 381 ± 26 814	0.59	55 360 ± 54 167	0.38
L	108 330 ± 1 357 514	84 180 ± 26 242	0.56	36 168 ± 29 545	0.35
P-value (R vs L)	>0.99	0.64		0.99	
FT (s)					
V	11 ± 8	15 ± 6	0.05	10 ± 5	0.89
R	14 ± 7	21 ± 17	0.35	12 ± 7	0.48
L	12 ± 5	16 ± 8	0.23	10 ± 4	0.62
P-value (R vs L)	0.89	0.99		0.94	
WoR (a.u.)					
V	2198 ± 3187	1644 ± 1725	0.87	2899 ± 3899	0.92
R	964 ± 679	658 ± 806	0.46	643 ± 656	0.38
L	912 ± 801	693 ± 694	0.68	526 ± 352	0.48
P-value (R vs L)	0.82	0.98		0.76	

Absolute T-CEUS parameters: *P*-values are given for absolute side differences (column, *P*-value proportion) and absolute changes over time-points (*P*-value time-point, row).

FT: fall time; L: left hemisphere; mTT: mean-transit-time; PE: peak enhancement; POST: after skin suture; PRAE: before skin incision; R: right hemisphere; RT: rise time; T-CEUS: transfontanellar contrast-enhanced ultrasound; TTP: time-to-peak; V: superior sagittal venous sinus; UCP: unilateral cerebral perfusion; WiAUC: wash-in-area-under-the-curve; WiPI: wash-in perfusion index; WiR: wash-in rate; WiWoAUC: wash-in-wash-out-area-under-the-curve; WoAUC: wash-out-area-under-the-curve; WoR: wash-out rate.

Table 3: Relative T-CEUS parameters

Parameter	PRAE (%)	UCP (%)	POST (%)
PE (a.u.)			
R	55.2 ± 11.5	50.8 ± 5.5	52.4 ± 12.8
L	44.8 ± 11.5	49.2 ± 5.5	47.6 ± 12.8
P-value (R vs L)	0.25	0.90	0.83
WiAUC (a.u.)			
R	55.2 ± 1.5	53.1 ± 8.7	50.5 ± 14.0
L	44.8 ± 11.5	46.9 ± 8.7	49.5 ± 14.0
P-value (R vs L)	0.20	0.38	>0.99
RT (s)			
R	47.5 ± 11.8	52.2 ± 7.3	48.2 ± 3.7
L	52.5 ± 11.8	47.8 ± 7.3	51.8 ± 3.7
P-value (R vs L)	0.79	0.52	0.16
mTT (s)			
R	37.3 ± 20.8	57.8 ± 23.3	45.2 ± 21.7
L	62.7 ± 20.8	42.2 ± 23.3	54.8 ± 21.7
P-value (R vs L)	0.08	0.43	0.74
TTP (s)			
R	47.8 ± 9.9	52.6 ± 6.6	49.0 ± 4.2
L	52.5 ± 11.8	47.4 ± 6.6	51.0 ± 4.2
P-value (R vs L)	0.76	0.31	0.68
WiR (a.u.)	*ns*	*ns*	*ns*
R	55.4 ± 16.3	49.2 ± 10.3	53.4 ± 14.2
L	44.6 ± 16.3	50.8 ± 10.3	46.6 ± 14.2
P-value (R vs L)	0.50	0.98	0.70
WiPI (a.u.)			
R	55.0 ± 10.7	51.0 ± 6.0	52.2 ± 13.2
L	45.0 ± 10.7	49.4 ± 6.0	47.8 ± 13.2
P-value (R vs L)	0.23	0.88	0.87
WoAUC (a.u.)			
R	53.2 ± 6.8	46.2 ± 9.5	54.4 ± 6.4
L	46.8 ± 6.8	53.8 ± 9.5	45.6 ± 6.4
P-value (R vs L)	0.28	0.47	0.07
WiWoAUC (a.u.)			
R	53.1 ± 6.2	46.9 ± 8.0	54.6 ± 6.4
L	46.9 ± 6.2	53.2 ± 8.0	45.4 ± 6.4
P-value (R vs L)	0.23	0.50	0.06
FT (s)			
R	51.7 ± 8.1	47.8 ± 9.2	48.8 ± 4.7
L	48.3 ± 8.1	52.2 ± 9.2	51.2 ± 4.7
P-value (R vs L)	0.84	0.81	0.72
WoR (a.u.)			
R	50.0 ± 12.3	50.6 ± 11.4	57.6 ± 5.9
L	50.0 ± 12.3	49.4 ± 11.4	42.4 ± 5.9
P-value	>0.99	>0.99	<0.01

P-Value: Relation of T-CEUS parameters (%) between hemispheres.

FT: fall time; L: left hemisphere; mTT: mean-transit-time; PE: peak enhancement; POST: after skin suture; PRAE: before skin incision; R: right hemisphere; RT: rise time; T-CEUS: transfontanellar contrast-enhanced ultrasound; TTP: time-to-peak; UCP: unilateral cerebral perfusion; V: superior sagittal venous sinus; WiAUC: wash-in-area-under-the-curve; WiPI: wash-in perfusion index; WiR: wash-in rate; WiWoAUC: wash-in-wash-out-area-under-the-curve; WoAUC: wash-out-area-under-the-curve; WoR: wash-out rate.

parameters were found, except for a higher relative 'wash-out-rate' on the right hemisphere after skin suture (58 ± 6% vs 42 ± 6%, *P* = 0.0013) (Fig. 3).

When compared to ipsilateral baseline levels, significance was found during UCP regarding an increase of 'time-to-peak' in both hemispheres (right: *P* = 0.0403 and left: *P* = 0.0286) and 'rise time' in the right hemisphere (*P* = 0.0277) (Table 2 and 3).

Clinical outcome measures

No significant differences of NIRS-derived saturations between hemispheres were found (Fig. 4A).

When compared to baseline values, a significant decrease of lower body NIRS levels was found during UCP, which normalized after surgery (PRAE: 76 ± 9%, UCP: 44 ± 23%, POST: 69 ± 6%; *P* = 0.0028) (Fig. 4B).

Values of central venous pressure did not differ significantly throughout surgery (PRAE: 9 ± 5 mmHg, UCP: 12 ± 4 mmHg, POST: 10 ± 5 mmHg) (Fig. 5A).

When compared to baseline values, a significant increase of mean arterial blood pressure was found during UCP (PRAE: 48 ± 11 mmHg vs UCP: 58 ± 13 mmHg; *P* = 0.0270), which normalized after surgery (POST: 51 ± 13 mmHg) (Fig. 5B).

When compared to baseline values, a significant increase of heart rate was found throughout surgery (PRAE: 111 ± 12/min vs UCP: 123 ± 20/min; *P* = 0.0308 and vs POST: 130 ± 14/min; *P* = 0.0005) (Fig. 5C).

DISCUSSION

Safety of REEEA is warranted over years of clinical praxis, but cerebral perfusion hardly measurable during the procedure. In this study, T-CEUS provided evidence for equal distribution of contrast agent in both hemispheres, hence for an equal cerebral perfusion during REEEA. We believe that inhomogeneous distribution of wash-out-rate in favour of the right hemispheres after surgery could be explained either by an unrestricted run-off of arterial blood flow from the left hemisphere into the lower body similarly to a 'steal phenomenon', or by an impaired venous outflow resulting from swelling and tissue oedema with increased venous resistance. Both direct implications of surgery should normalize in progress.

It is interesting, that during UCP significant differences in perfusion were found only in regard to the ipsilateral hemisphere when compared to baseline levels. When the aortic arch is clamped complete cardiac output is ejected into the innominate artery. Thus, global cerebral perfusion is increased by the intact circle of Willis connecting the left hemisphere to the antegrade flow from the right (increased time-to-peak in both hemispheres). Due to UCP, we consider that particularly the right hemisphere is exposed to a higher resistance with outflow via the circle of Willis leading to altered cerebral flow dynamics, such as slower increase of the T-CEUS signals (rise time in the right hemisphere).

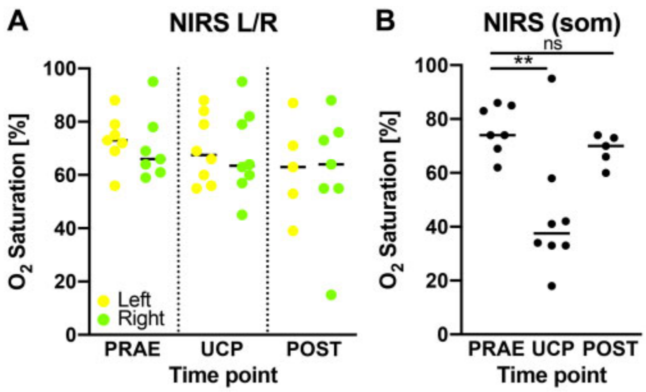

Figure 4: NIRS measurements during surgical procedures. (**A**) Relative distribution of transfontanellar contrast-enhanced ultrasound signals between hemispheres during surgery. (**B**) Absolute NIRS measurements of lower body. L: left; NIRS: near-infrared spectroscopy; ns: non-significant; **p<0.01; POST: after skin closure; PRAE: before skin incision; R: right; UCP: unilateral cerebral perfusion.

The hypothesis of homogenous cerebral perfusion during REEEA is underlined by stable regional cerebral saturations in both hemispheres, despite varying heart rate and right radial artery pressures throughout surgery. Based on NIRS-data, other groups have demonstrated that UCP provides comparable blood flows and oxygenation to both cerebral hemispheres during congenital aortic arch surgery [1, 15, 16]. Hoffman *et al.* [16] stated that perioperative cerebral oxygenation assessed by NIRS can detect hypoxic–ischaemic conditions associated with injury and reduced neurodevelopmental performance. In addition, NIRS can be used as an online non-invasive tool for intraoperative regional perfusion measurement, which corresponds well to patient's haemodynamic status. However, NIRS only provides information derived penetrating light at a maximum of 2–3 cm of depth, which predominantly represents the cortex tissue. In turn [17], T-CEUS also captures signals from the entire cross-section of the brain but does not provide a continuous perioperative application due to its implication with an ultrasound contrast agent. Currently, quantification of measurements also requires postprocessing and comprehensive data interpretation. Therefore, T-CEUS and NIRS generate different partially complementary information. Whereas NIRS serves as a surrogate for regional cardiac output, with T-CEUS you can 'see' and quantify global tissue perfusion in an entire organ. As a result, its conclusiveness regarding perfusion may be much more precise.

The question could be raised whether the results from REEEA can be extrapolated to complete arch repair, when UCP is secured by CPB and direct cannulation of the innominate artery or by cannulating a polytetrafluorethylene tube anastomosed to the vessel [1–3, 15, 18]. Due to the variety of technical aspects associated with aortic arch repair where the extend of perfusion, target temperature and method of blood gas management are diverse, results from a well standardized procedure like REEEA can be adopted only in parts [19–21].

Limitations

Limitations of the study are inherent to its single-centre design and small sample size. Concerning the institutional policy to operate on critical coarctation soon after diagnosis, surgery is being

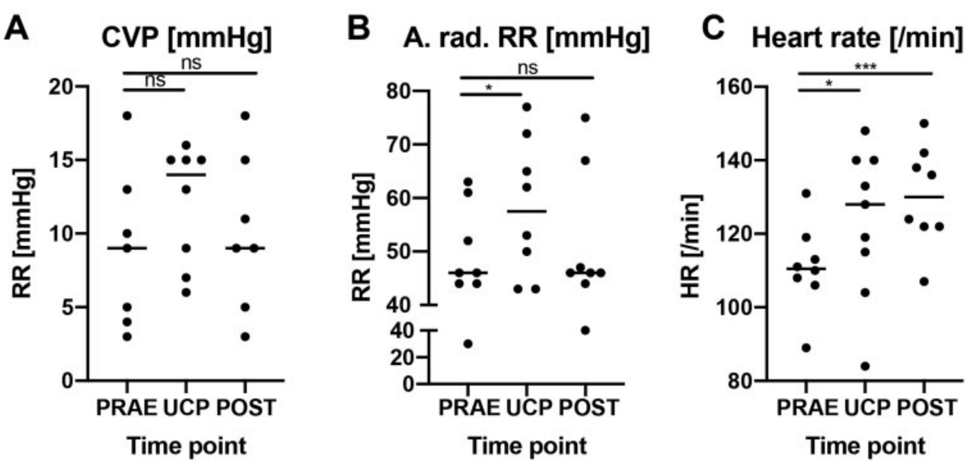

Figure 5: Circulatory parameters during surgical procedures. (**A**) CVP during procedures. (**B**) Blood pressure measured via radial artery during procedures. (**C**) HR during surgical procedures. CVP: central venous pressure; HR: heart rate; ns: non-significant; POST: after skin closure; PRAE: before skin incision; RR: Riva Rocci (blood pressure); UCP: unilateral cerebral perfusion. *p<0.05, ***p<0.001.

performed often after regular clinical working ours. Therefore, the study period was prolonged to guarantee completeness of the scientific team. Practical problems such as small imaging windows due to small fontanelles may limit imaging results. The imaging method still needs further standardization and validation with clinical and neurological outcome.

CONCLUSIONS

Using T-CEUS at different stages of REEEA, a homogenous distribution of contrast agent among bilateral cerebral tissue was assessed. Even during UCP an adequate cerebral blood flow was depicted. T-CEUS can be applied for the postprocedural evaluation of cerebral perfusion during various kinds of aortic arch surgery in infants with open fontanelle.

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Author contributions

André Rüffer: Conceptualization; Investigation; Methodology; Project administration; Writing—original draft; Writing—review & editing. **Ferdinand Knieling:** Data curation; Formal analysis; Funding acquisition; Software; Visualization. **Robert Cesnjevar:** Project administration; Supervision; Writing—review & editing. **Adrian Regensburger:** Data curation; Funding acquisition; Software. **Ariawan Purbojo:** Data curation; Writing—review & editing. **Sven Dittrich:** Project administration; Writing—review & editing. **Frank Münch:** Data curation. **Joachim Woelfle:** Writing—review & editing. **Jörg Jüngert:** Conceptualization; Data curation; Funding acquisition; Investigation; Software; Validation; Visualization; Writing—review & editing.

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REFERENCES

[1] Andropoulos DB, Stayer SA, McKenzie ED, Fraser CD Jr. Regional low-flow perfusion provides comparable blood flow and oxygenation to both cerebral hemispheres during neonatal aortic arch reconstruction. J Thorac Cardiovasc Surg 2003;126:1712–17.

[2] Andropoulos DB, Stayer SA, McKenzie ED, Fraser CD Jr. Novel cerebral physiologic monitoring to guide low-flow cerebral perfusion during neonatal aortic arch reconstruction. J Thorac Cardiovasc Surg 2003;125: 491–9.

[3] Ruffer A, Tischer P, Munch F, Purbojo A, Toka O, Rascher W *et al.* Comparable cerebral blood flow in both hemispheres during regional cerebral perfusion in infant aortic arch surgery. Ann Thorac Surg 2017; 103:178–85.

[4] Amato JJ, Rheinlander HF, Cleveland RJ. A method of enlarging the distal transverse arch in infants with hypoplasia and coarctation of the aorta. Ann Thorac Surg 1977;23:261–3.

[5] Backer CL, Mavroudis C, Zias EA, Amin Z, Weigel TJ. Repair of coarctation with resection and extended end-to-end anastomosis. Ann Thorac Surg 1998;66:1365–70; discussion 70–1.

[6] Conte S, Lacour-Gayet F, Serraf A, Sousa-Uva M, Bruniaux J, Touchot A *et al.* Surgical management of neonatal coarctation. J Thorac Cardiovasc Surg 1995;109:663–74; discussion 74–5.

[7] Dodge-Khatami A, Backer CL, Mavroudis C. Risk factors for recoarctation and results of reoperation: a 40-year review. J Card Surg 2000;15: 369–77.

[8] Simon BV, Swartz MF, Orie JM, Adams HR, Seltzer LE, Angona RE *et al.* Neurodevelopmental delay after the neonatal repair of coarctation and arch obstruction. Ann Thorac Surg 2019;108:1416–22.

[9] Hwang M, De Jong RM Jr, Herman S, Boss R, Riggs B, Tekes-Brady A *et al.* Novel contrast-enhanced ultrasound evaluation in neonatal hypoxic ischemic injury: clinical application and future directions. J Ultrasound Med 2017;36:2379–86.

[10] Knieling F, Strobel D, Rompel O, Zapke M, Menendez-Castro C, Wolfel M *et al.* Spectrum, applicability and diagnostic capacity of contrast-enhanced ultrasound in pediatric patients and young adults after intravenous application—a retrospective trial. Ultraschall Med 2016;37: 619–26.

[11] Hwang M, Barnewolt CE, Jungert J, Prada F, Sridharan A, Didier RA. Contrast-enhanced ultrasound of the pediatric brain. Pediatr Radiol 2021. doi: 10.1007/s00247-021-04974-4.

[12] Kastler A, Manzoni P, Chapuy S, Cattin F, Billon-Grand C, Aubry S *et al.* Transfontanellar contrast enhanced ultrasound in infants: initial experience. J Neuroradiol 2014;41:251–8.

[13] Knieling F, Ruffer A, Cesnjevar R, Regensburger AP, Purbojo A, Dittrich S *et al.* Transfontanellar contrast-enhanced ultrasound for monitoring brain perfusion during neonatal heart surgery. Circ Cardiovasc Imaging 2020;13:e010073.

[14] Dave HH, Buechel ER, Pretre R. Muscle-sparing extrapleural approach for the repair of aortic coarctation. Ann Thorac Surg 2006;81: 243–8.

[15] Kwak JG, Kim WH, Oh AY, Yoon TG, Kim HS, Chae JH *et al.* Is unilateral brain regional perfusion neurologically safe during congenital aortic arch surgery? Eur J Cardiothorac Surg 2007;32:751–5.

[16] Hoffman GM, Brosig CL, Mussatto KA, Tweddell JS, Ghanayem NS. Perioperative cerebral oxygen saturation in neonates with hypoplastic left heart syndrome and childhood neurodevelopmental outcome. J Thorac Cardiovasc Surg 2013;146:1153–64.

[17] Dix LM, van Bel F, Lemmers PM. Monitoring cerebral oxygenation in neonates: an update. Front Pediatr 2017;5:46.

[18] Asou T, Kado H, Imoto Y, Shiokawa Y, Tominaga R, Kawachi Y *et al.* Selective cerebral perfusion technique during aortic arch repair in neonates. Ann Thorac Surg 1996;61:1546–8.

[19] Dent CL, Spaeth JP, Jones BV, Schwartz SM, Glauser TA, Hallinan B *et al.* Brain magnetic resonance imaging abnormalities after the Norwood procedure using regional cerebral perfusion. J Thorac Cardiovasc Surg 2006;131:190–7.

[20] Goldberg CS, Bove EL, Devaney EJ, Mollen E, Schwartz E, Tindall S *et al.* A randomized clinical trial of regional cerebral perfusion versus deep hypothermic circulatory arrest: outcomes for infants with functional single ventricle. J Thorac Cardiovasc Surg 2007; 133:880–7.

[21] Hanley FL. Religion, politics. . .deep hypothermic circulatory arrest. J Thorac Cardiovasc Surg 2005;130:1236.