Circulation: Cardiovascular Imaging

RESEARCH LETTER

# Transfontanellar Contrast–Enhanced Ultrasound for Monitoring Brain Perfusion During Neonatal Heart Surgery

**Ferdinand Knieling, MD**
**André Rüffer, MD**
**Robert Cesnjevar, MD**
**Adrian P. Regensburger, MD**
**Ariawan Purbojo, MD**
**Sven Dittrich, MD**
**Frank Münch, MS**
**Antje Neubert, PhD**
**Sebastian Meyer, PhD**
**Deike Strobel, MD**
**Wolfgang Rascher, MD**
**Joachim Woelfle, MD**
**Jörg Jüngert, MD**

While current mortality rates for neonatal heart surgery are low,[1] there is significant concern about the effects of cardiopulmonary bypass (CPB) on the neonatal brain and later neurodevelopmental impairments.[2] To date, no good techniques are available to study the effects of neonatal heart surgery on brain perfusion.

The aim of this study is to investigate the potential of transfontanellar contrast–enhanced ultrasound (T-CEUS) for quantitative assessment of cerebral blood flow in different phases of neonatal cardiac surgery with and without CPB.

In a monocentric, explorative feasibility study n=5 patients with coarctation of the aorta (CoA) and n=7 patients with transposition of great arteries (TGA) were included (URL: http://www.clinicaltrials.gov. Unique identifier: NCT03215628) from September 18, 2017, to March 14, 2019. The study was approved by the local ethics committee (*20_17B*). Informed consent for the study and the off-label use of the ultrasound contrast agent were obtained from all legal guardians. The data that support the findings of this study are available from the corresponding author on reasonable request. For the CoA group, 3 different time points were selected for T-CEUS imaging: before, during (placement of aortic clamps), and after surgery. For the TGA group, 5 different time points were recorded: before, during high flow of the CPB at 37°C, high flow at 28°C, low flow at 28°C, and after surgery. All patients were hemodynamically stable and without the need of catecholamine therapy before surgery. In total, n=50 measurements (n=15 for CoA and n=35 TGA) were performed directly after reaching the respective stage of surgery. For imaging, a mobile high-end ultrasound system (Mindray, Zonare ZS 3, Zonare Medical System Inc, Mountain View, CA; Software Version 7.5) equipped with a curved array (C9-3/3) was used. The probe was directly positioned at the great fontanelle and a middle coronal imaging plane was kept constant during acquisition. The ultrasound contrast agent (SonoVue, Bracco, Milan, Italy, mean diameter: 2.5 µm)[3] was injected intravenously followed by a flush of 2 mL NaCl 0.9%.[4] Injections were only performed after complete visible clearance of circulating microbubbles at a mean interval of 18.9 minutes between the different surgical stages. In the TGA group, the ultrasound contrast agent dose was adjusted with a compensation weight of 1 kg to the total body weight because of the priming volume of 148 mL in the CPB.

In a secondary software-based analysis, the regions of interests were delineated by 2 independent blinded investigators using VueBox (Version 7.1, Bracco Suisse SA, Plan-lesouates, Switzerland). By this, 11 dynamic flow parameters (eg, rise time [RT] and time-to-peak as measures for the time required for a contrast bolus to accumulate to a maximum in a specific tissue region) were generated for subsequent analyses. Differences between groups were tested with repeated measures 1-way ANOVA and Dunnett multiple comparisons test.



*Drs Knieling and Rüffer contributed equally to this work.



https://www.ahajournals.org/journal/circimaging

In the CoA group undergoing end-to-end anastomosis, the total duration from first to last T-CEUS imaging was 99±18 minutes. RT of the right hemisphere was 4.01±1.40 s before surgery, 5.13±1.95 s (*P*=0.23) during intervention, and 3.60±1.37 s (*P*=0.79) after surgery (Figure [A] and [B]). Comparable results were obtained regarding TPP and in the left hemispheres. Furthermore, no side differences (left versus right) were observed. In addition, none of the other analyzed parameters showed statistically significant differences. In comparison, measurements in TGA patients undergoing arterial switch surgery required 311±45 minutes from first to last T-CEUS imaging. At the beginning, RT of the right hemispheres was 4.30±1.71 s and increased to 17.77±8.80 s (*P*<0.0001) during low flow 28°C. Comparable results were obtained for the left hemispheres, and no side differences (left versus right) were observed. Alterations of time-to-peak were similar to RT: 5.21±1.62 s before surgery and 23.57±9.93 s (*P*<0.0001) during low flow 28°C (Figure [C] and [D]). Interclass correlation, as indicator of reliability of the T-CEUS quantifications, were 0.99 (95% CI, 0.98–0.99) for RT and 0.99 (95% CI, 0.99–0.99) for time-to-peak, respectively.

In the present study, 2 different congenital heart diseases, CoA and TGA, were included. Our approach showed no changes in the T-CEUS parameters during CoA surgery, while these changed significantly with the use of a CPB during reduced flow rates. Therefore, this real-time modality can be particularly useful to quantitatively monitor cerebral perfusion dynamics during neonatal heart surgery. However, no differences were seen in the side proportion of left and right hemispheres. Moreover, no side effects of the ultrasound contrast agent were documented during application in the surgical procedures and subsequent intraoperative monitoring. Our study is the first description of the potential use of contrast-enhanced ultrasound to monitor brain perfusion during CPB. Our results are promising and tie up with earlier studies looking into the diagnostic use of contrast-enhanced ultrasound during extracorporeal life support.[5]

In conclusion, T-CEUS is a technique that could be used to study cerebral perfusion during neonatal heart surgery. Our preliminary results need to be verified

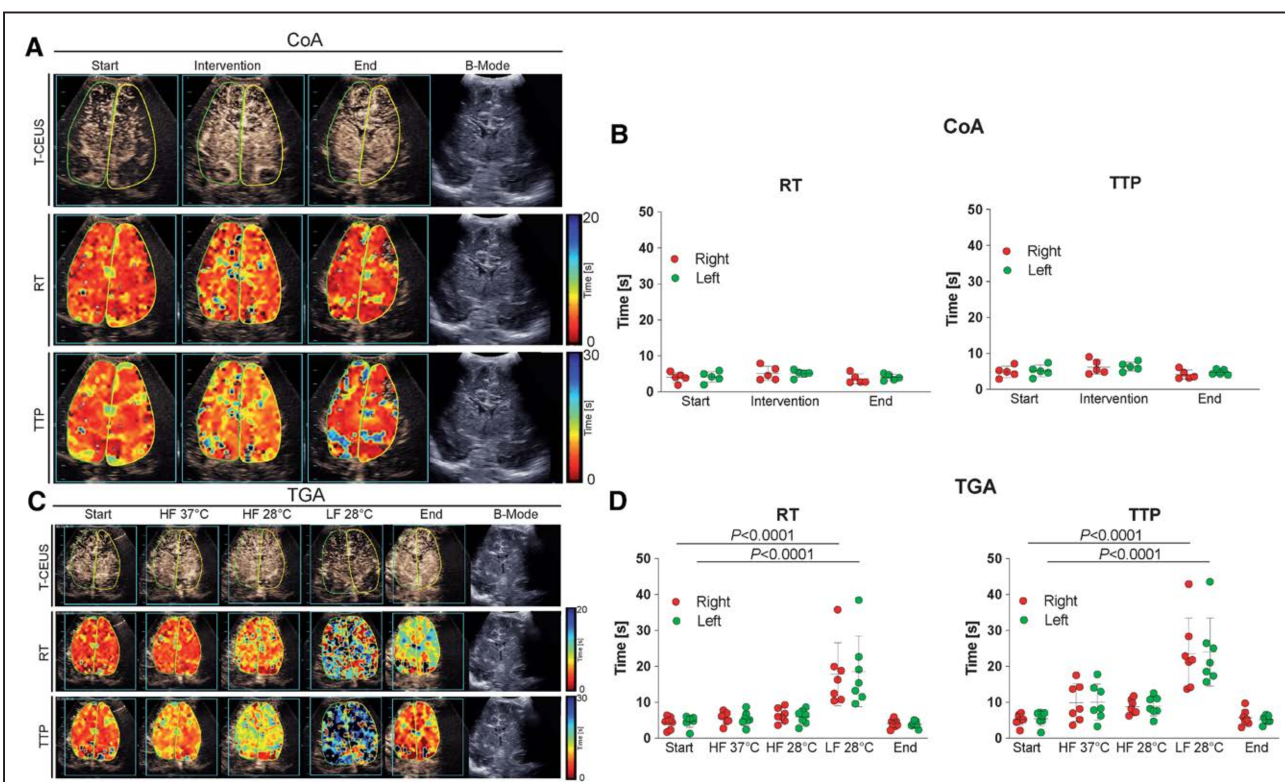


**Figure. Changes of perfusion during coarctation of the aorta (CoA) and transposition of great arteries (TGA) surgery.**
**A**, Representative transfontanellar contrast–enhanced ultrasound (T-CEUS) images of a CoA patient (**upper** row), color-coded map for rise time (RT; **middle** row), and color-coded map for time-to-peak (TTP; **lower** row). Start indicates begin of surgery; Intervention, aortic clamps in place; and end, End of surgery. **B**, Quantification of RT and TTP indicating constant perfusion during surgical procedures. **C**, Representative T-CEUS images of a TGA patient (**upper** row), color-coded map for RT (**middle** row), and color-coded map for TTP (**lower** row). HF 37°C indicates high flow of cardiopulmonary bypass at 37°C body temperature; HF 28°C, high flow of cardiopulmonary bypass at 28°C body temperature; LF 28°C, low flow (≈30%) of cardiopulmonary bypass at 28°C body temperature; and End, end of surgery. **D**, Quantification of RT and TTP during arterial switch surgery. Increased RT and TTP values, in contrast to the CoA group, indicate reduced perfusion during low flow (LF) 28°C when compared with baseline.
Scale bars indicate 1 cm steps; dots, measurements from individual patients; bars, mean±SD; red, right hemisphere; and green, left hemisphere.

by additional data including correlations of cerebral perfusion and clinical neurodevelopmental outcomes.

## ARTICLE INFORMATION

### Correspondence

Ferdinand Knieling, MD, Pediatric Experimental and Translational Imaging Laboratory (PETI_Lab), Department of Pediatrics and Adolescent Medicine, Friedrich-Alexander-University (FAU) of Erlangen-Nuremberg, Loschgestraße 15, 91054 Erlangen, Germany. Email ferdinand.knieling@uk-erlangen.de

### Affiliations

Department of Pediatrics and Adolescent Medicine (F.K., A.P.R., A.N., W.R., J.W., J.J.), Department of Congenital Heart Surgery (A.R., R.C., A.P., F.M.), Department of Pediatric Cardiology (S.D.), and Department of Medicine 1 (D.S.), University Hospital Erlangen and Institute of Medical Informatics, Biometry, and Epidemiology (IMBE) (S.M.), Friedrich-Alexander-University (FAU) of Erlangen-Nuremberg, Erlangen, Germany.

### Sources of Funding

The study was funded by the German Society for Ultrasound in Medicine (Deutsche Gesellschaft für Ultraschall in der Medizin [DEGUM] to Drs Knieling and Jüngert). Drs Knieling and Regensburger received support from the Interdisciplinary Center for Clinical Research (IZKF). Dr Knieling was supported by Erlangen Start-up and Young Talent Funding (ELAN) fund Erlangen.

### Disclosures

None.

## REFERENCES

1. Raissadati A, Nieminen H, Haukka J, Sairanen H, Jokinen E. Late causes of death after pediatric cardiac surgery: a 60-Year Population-Based Study. *J Am Coll Cardiol*. 2016;68:487–498. doi: 10.1016/j.jacc.2016.05.038
2. Marino BS, Lipkin PH, Newburger JW, Peacock G, Gerdes M, Gaynor JW, Mussatto KA, Uzark K, Goldberg CS, Johnson WH Jr, et al; American Heart Association Congenital Heart Defects Committee, Council on Cardiovascular Disease in the Young, Council on Cardiovascular Nursing, and Stroke Council. Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association. *Circulation*. 2012;126:1143–1172. doi: 10.1161/CIR.0b013e318265ee8a
3. Schneider M. SonoVue, a new ultrasound contrast agent. *Eur Radiol*. 1999;9(suppl 3):S347–S348. doi: 10.1007/pl00014071
4. Knieling F, Strobel D, Rompel O, Zapke M, Menendez-Castro C, Wölfel M, Schulz J, Rascher W, Jüngert J. Spectrum, applicability and diagnostic capacity of contrast-enhanced ultrasound in pediatric patients and young adults after intravenous application - a Retrospective Trial. *Ultraschall Med*. 2016;37:619–626. doi: 10.1055/s-0042-108429
5. Bennett CE, Tweet MS, Michelena HI, Schears GJ, Mulvagh SL. Safety and feasibility of contrast echocardiography for ECMO evaluation. *JACC Cardiovasc Imaging*. 2017;10:603–604. doi: 10.1016/j.jcmg.2016.05.004