Transkranielle Dopplersonographie (TCD)

bei Sichelzellkrankheit (SCD)

HÄMATOLOGIE HEUTE
ULM

24.04.2015 | Matthias C. Schaal – Universitätsklinikum Ulm, Klinik für Kinder- und Jugendmedizin

TCD bei SCD

- Grundlagen der Dopplersonographie
- Hintergrund der transkraniellen Dopplersonographie bei Sichelzellkrankheit – Ablauf der Untersuchung und Konsequenzen des Screenings
- Eigene Erfahrungen aus Ulm

Grundlagen der Dopplersonographie

Christian Doppler
29.11.1803 - 17.03.1853

„Über das farbige Licht der Doppelsterne und einiger anderer Gestirne des Himmels“

25.05.1842

Abhandlungen der k. böhm. Gesellschaft der Wissenschaften (V. Folge, Bd. 2, S. 465-482)

Grundlagen der Dopplersonographie

- Doppler-Effekt: zeitliche Stauchung bzw. Dehnung eines Signals bei Veränderungen des Abstands zwischen Sender und Empfänger während der Dauer des Signals.

- Vereinfachte Dopplerformel (zulässig, wenn die Geschwindigkeit des bewegten Objektes deutlich geringer als die Lichtgeschwindigkeit ist):

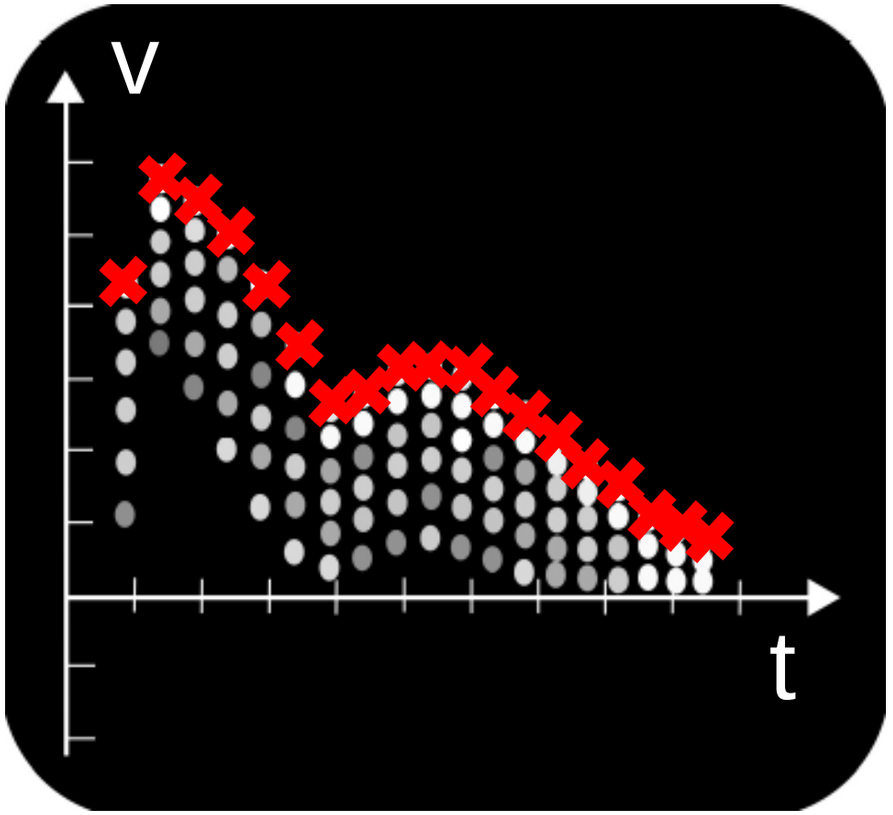
$$Frequenzverschiebung\ (Hz) = \frac{Geschwindigkeit\ \left(\frac{m}{s}\right) \times Ursprungsfrequenz\ (Hz)}{Schallgeschwindigkeit\ \left(\frac{m}{s}\right)}$$

Grundlagen der Dopplersonographie

- Anwendung in der Medizin:
  Frequenzänderung eines Ultraschallstrahles durch sich bewegende korpuskuläre Bestandteile (Erythrozyten) des Blutes = Dopplerfrequenz.

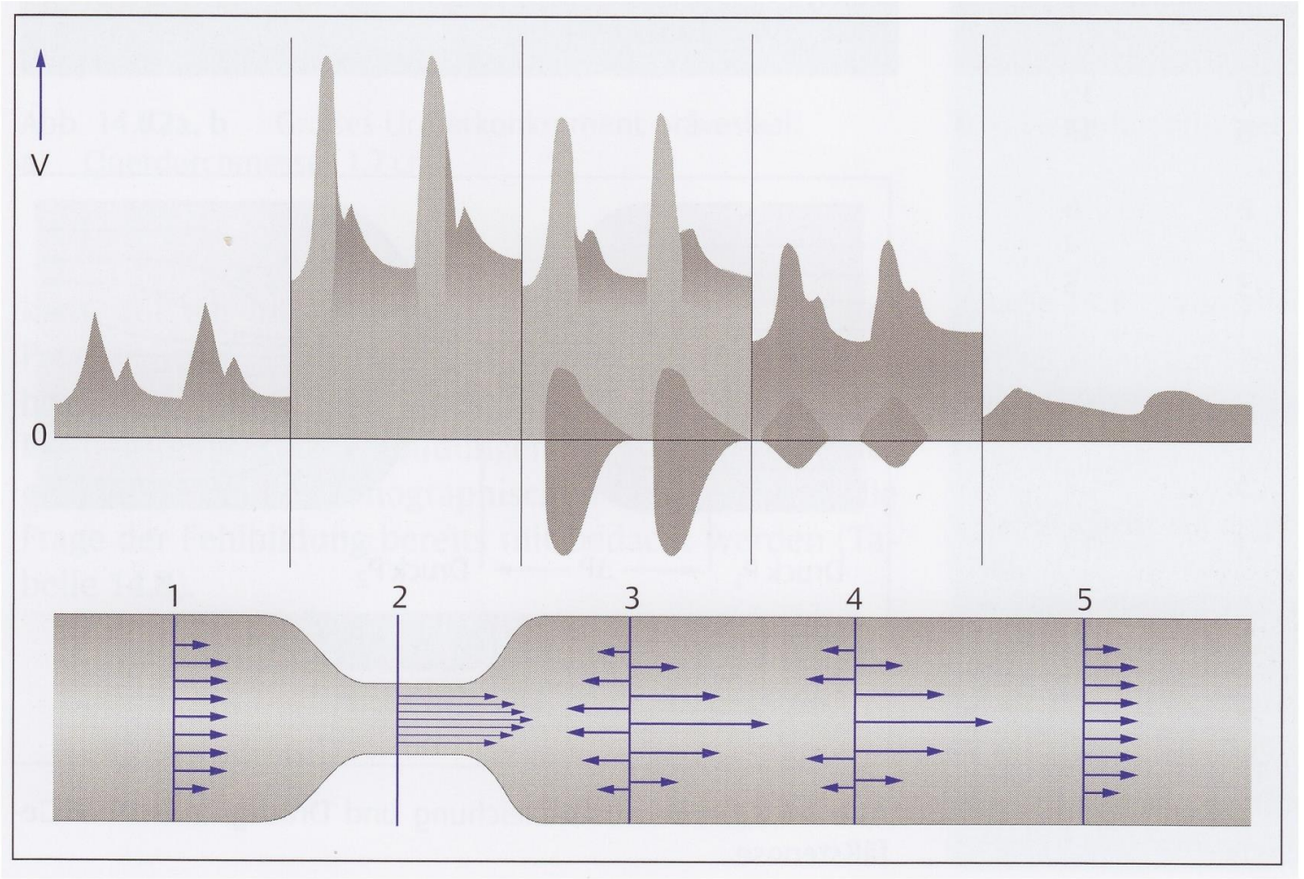
- Innerhalb des Gefäßes verschiedene Fließgeschwindigkeiten der einzelnen Erythrozyten – verschiedene Dopplerfrequenzen innerhalb eines Frequenzspektrums.

Grundlagen der Dopplersonographie



- TAMMx = Time Average Mean of the Maximum
- TAPV = Time Average Peak Velocity (Philips / ATL)
- TAMx (Siemens / Acuson)

Grundlagen der Dopplersonographie



Hofmann V, Deeg KH, Hoyer P. Ultraschalldiagnostik in Pädiatrie und Kinderchirurgie, Thieme 2005

TCD bei SCD

- Kumulative Inzidenz von cerebrovaskulären Komplikationen: 11% bis 20 Jahre, überwiegend ischämische Infarkte

Cerebrovascular Accidents in Sickle Cell Disease: Rates and Risk Factors

By Kwaku Ohene-Frempong, Steven J. Weiner, Lynn A. Sleeper, Scott T. Miller, Stephen Embury, John W. Moohr, Doris L. Wethers, Charles H. Pegelow, Frances M. Gill, and the Cooperative Study of Sickle Cell Disease

Blood, Vol 91, No 1 (January 1), 1998: pp 288-294

- Ursächlich: progressive Veränderungen, insbesondere Stenosen der distalen ICA sowie ACA und MCA
- Inflammation, exzessive Adhäsion von Blutzellen an das aktivierte Endothel, Ischämie-Reperfusionsschäden, Hyperkoagulabilität, Störungen der Gefäßtonusregulation

TCD bei SCD

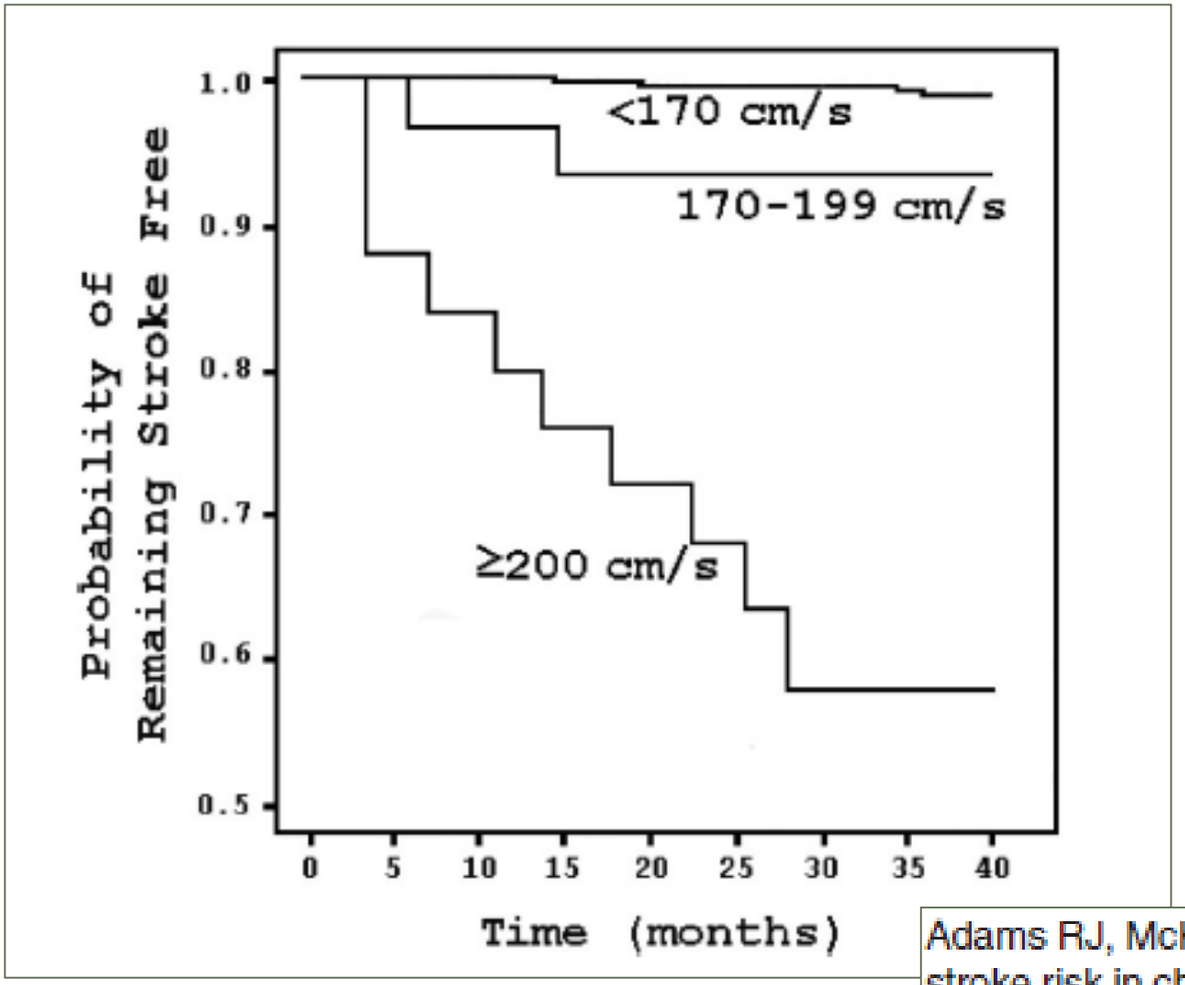
Detection of Cerebral Vasculopathy in Sickle Cell Disease Using Transcranial Doppler Ultrasonography and Magnetic Resonance Imaging

Case Report

Robert J. Adams, MD, Rune Aaslid, PhD, Taher El Gammal, MD,
Fenwick T. Nichols, MD, and Virgil McKie, MD

We describe a case of homozygous sickle cell anemia in which noninvasive transcranial Doppler ultrasonography and magnetic resonance imaging were used to detect angiographically documented occlusive lesions of intracranial arteries. (*Stroke* 1988;19:518–520)

TCD bei SCD



Adams RJ, McKie VC, Carl EM, et al. Long-term stroke risk in children with sickle cell disease screened with transcranial Doppler. *Ann Neurol.* 1997;42(5):699-704.

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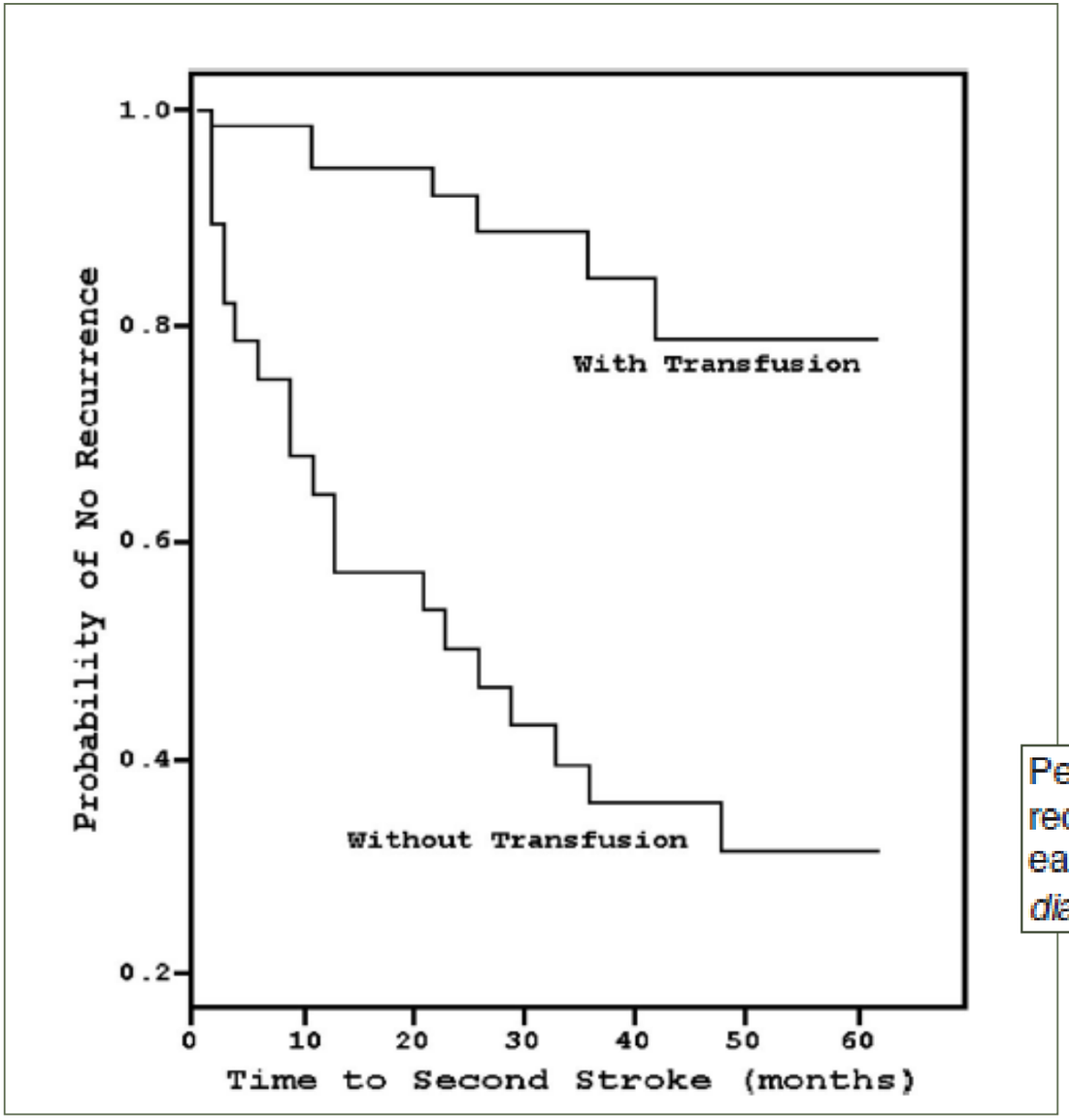

Pegelow CH, Adams RJ, McKie V, et al. Risk of recurrent stroke in patients with sickle cell disease treated with erythrocyte transfusions. *J Pediatr.* 1995;126(6):896-899.

TCD bei SCD

PREVENTION OF A FIRST STROKE BY TRANSFUSIONS IN CHILDREN WITH SICKLE CELL ANEMIA AND ABNORMAL RESULTS ON TRANSCRANIAL DOPPLER ULTRASONOGRAPHY

ROBERT J. ADAMS, M.D., VIRGIL C. MCKIE, M.D., LEWIS HSU, M.D., PH.D., BEATRICE FILES, M.D., ELLIOTT VICHINSKY, M.D., CHARLES PEGELOW, M.D., MIGUEL ABBOUD, M.D., DIANNE GALLAGHER, M.S., ABDULLAH KUTLAR, M.D., FENWICK T. NICHOLS, M.D., DUANE R. BONDS, M.D., AND DONALD BRAMBILLA, PH.D.

VARIABLE	TOTAL (N=130)	TRANSFUSION (N=63)	STANDARD CARE (N=67)
Follow-up (mo)			
Total	2550	1321	1229
Median	21.1	22.2	18.3
Mean ±SD	19.6±6.5	21.0±5.7	18.3±7.0
No. of strokes	12	1	11
Cerebral infarction	11	1	10
Intracerebral hematoma	1	0	1

Conclusions Transfusion greatly reduces the risk of a first stroke in children with sickle cell anemia who have abnormal results on transcranial Doppler ultrasonography. (N Engl J Med 1998;339:5-11.)

TCD bei SCD

bjh research paper

Elevated blood flow velocity in the anterior cerebral artery and stroke risk in sickle cell disease: extended analysis from the STOP trial

Janet L. Kwiatkowski,[1] Suzanne Granger,[2] Donald J. Brambilla,[2] R. Clark Brown,[3] Scott T. Miller[4] and Robert J. Adams[5] for the STOP Trial Investigators*

[1]*Division of Hematology, The Children's Hospital of Philadelphia and Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, PA,* [2]*New England Research Institutes, Watertown, MA,* [3]*Children's Healthcare of Atlanta/Emory University, Atlanta, GA,* [4]*SUNY-Downstate Medical Center/Kings County Hospital, Brooklyn, NY, and* [5]*Medical College of Georgia, Augusta, GA, USA*

Received 13 March 2006; accepted for publication 29 May 2006

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*The members of the STOP Trial Investigators are given in Appendix.

Summary

Elevated velocity in the internal carotid artery (ICA) or middle cerebral artery (MCA), detected by transcranial Doppler (TCD) ultrasonography, predicts an increased risk of stroke in children with sickle cell disease (SCD). Although strokes also occur in an anterior cerebral artery (ACA) distribution, the significance of elevated velocity in this vessel has not been determined previously. We assessed the effect of elevated ACA velocity on stroke risk using the results of the first adequate TCD study performed on 1975 children as part of The Stroke Prevention Trial in Sickle Cell Anemia (STOP). Elevated ACA velocity (≥170 cm/s) was associated with an increased risk of stroke ($P = 0{\cdot}0013$) after adjusting for the ICA/MCA classification. Among subjects with normal ICA/MCA velocity, the risk of stroke was more than 10-fold greater in those with elevated compared with normal ACA velocity (2·13 and 0·20 per 100 patient-years, respectively, $P < 0{\cdot}001$); risk more than doubled with elevated compared with normal ACA velocity in those already at high risk due to abnormal ICA/MCA findings (7·56 vs. 3·22 per 100 patient-years, $P = 0{\cdot}042$). Few of the strokes in those with elevated ACA velocity occurred in an ACA distribution, suggesting changes in blood flow velocity in anterior vessels may be associated with diffuse arterial disease or, alternatively, manifest collateral flow from compromised middle cerebral vessels.

Keywords: sickle cell disease, stroke, child, sickle cell radiology, vascular disease.

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Pediatr Radiol (2005) 35: 235–241
DOI 10.1007/s00247-005-1417-7

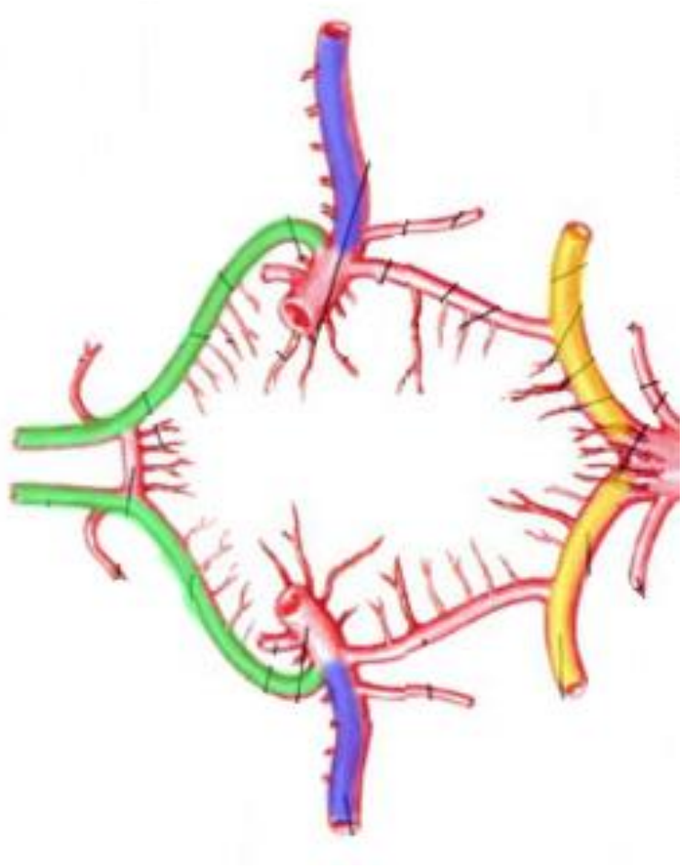
MINISYMPOSIUM

Dorothy Bulas

Screening children for sickle cell vasculopathy: guidelines for transcranial Doppler evaluation

TCD bei SCD

frontal



dorsal

Netter F. Atlas der Anatomie des Menschen, Novartis 1997

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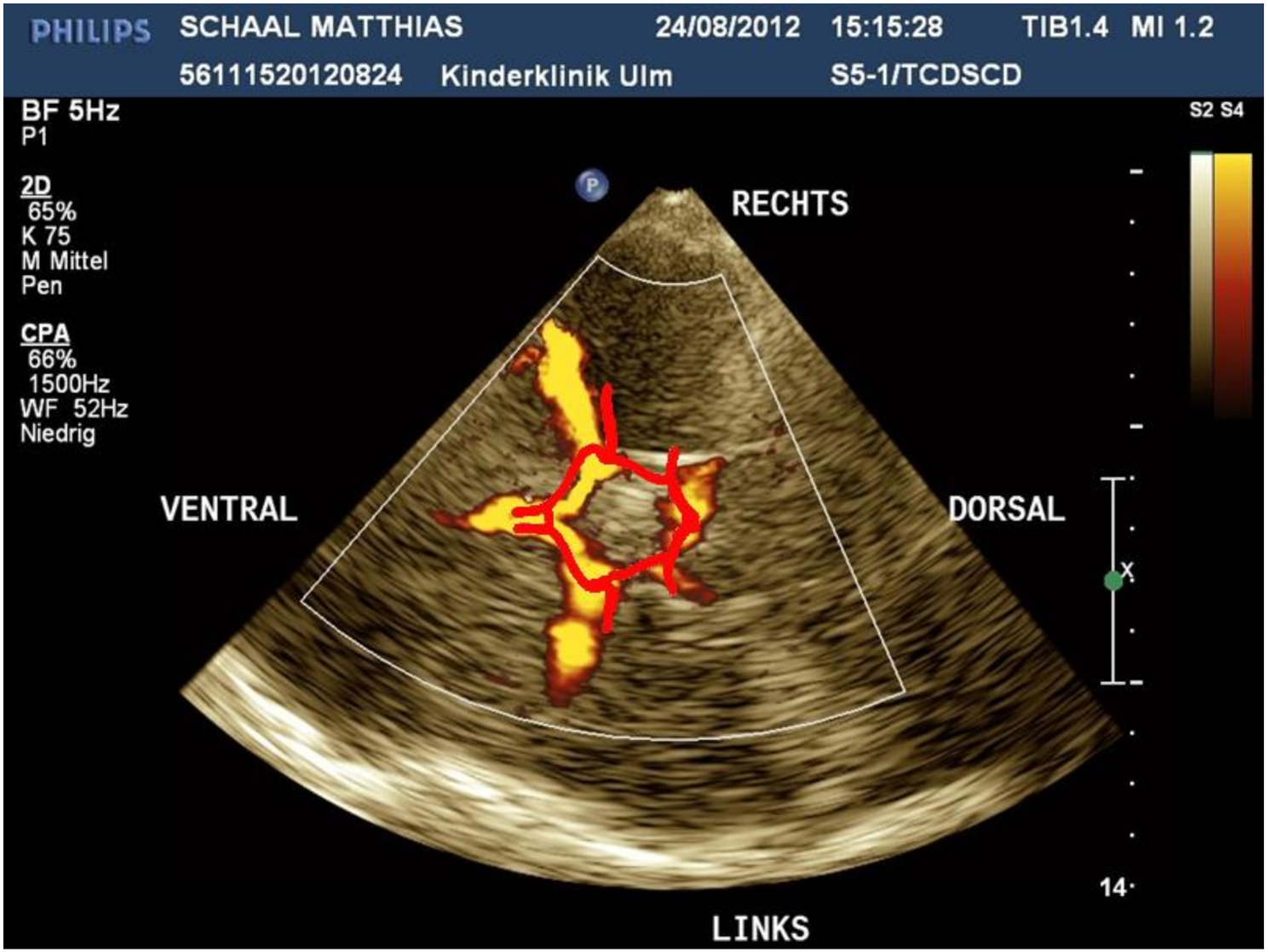
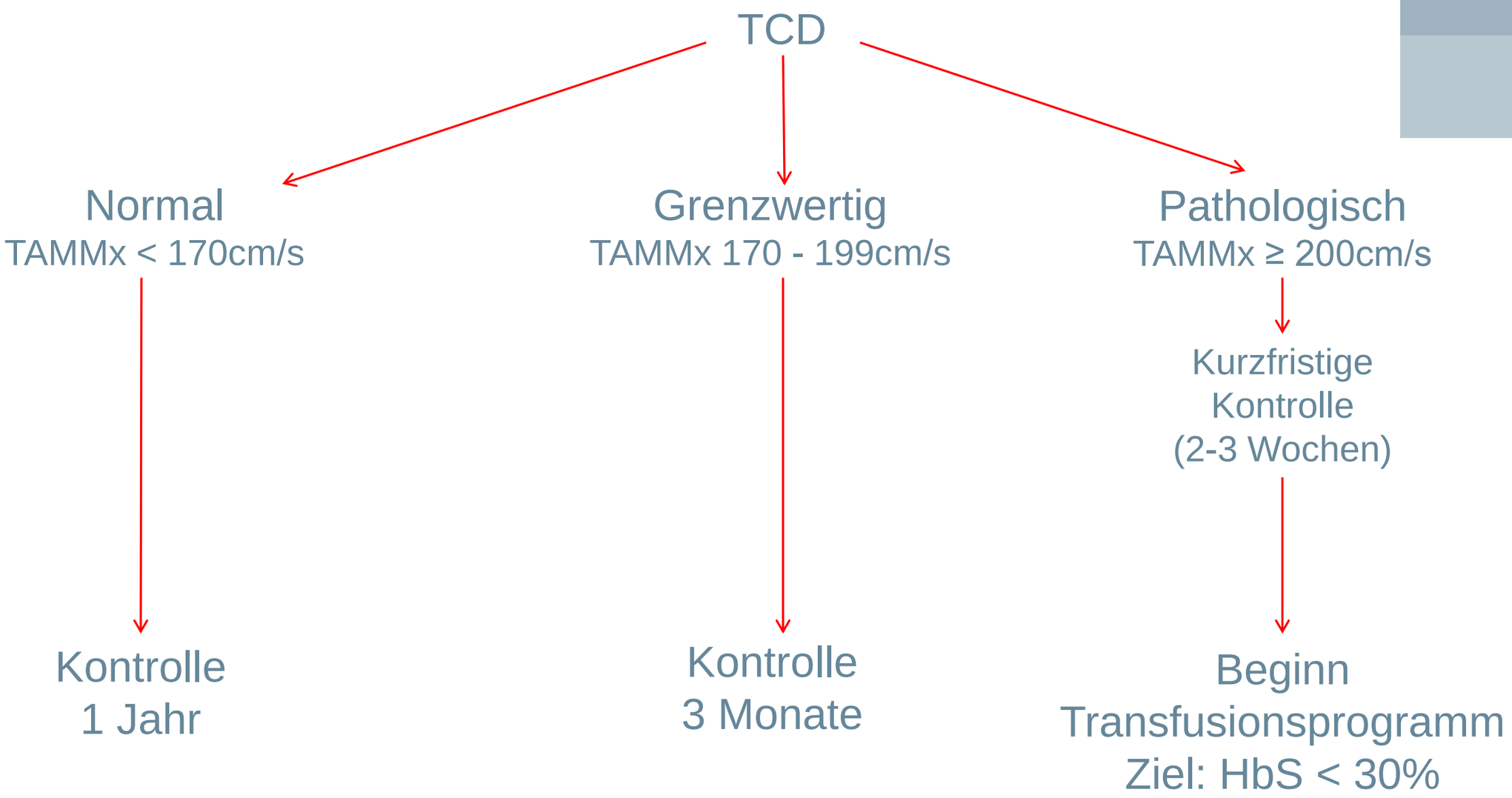

PHILIPS
SCHAAL MATTHIAS
24/08/2012
15:15:28
TIB1.4
MI 1.2
56111520120824
Kinderklinik Ulm
S5-1/TCDSCD
BF 5Hz
P1
2D
65%
K 75
M Mittel
Pen
CPA
66%
1500Hz
WF 52Hz
Niedrig
S2 S4
RECHTS
VENTRAL
DORSAL
LINKS
14

TCD bei SCD

- Patienten mit SCD-S/S oder SCD-S/ß⁰-Thalassämie
- 2. Lebensjahr bis 18 Jahre
- Keine Winkelkorrektur vornehmen!
- Zugangsweg transtemporal bds (erst links, dann rechts): Leitstruktur Pedunculi Cerebri
- Darstellung der A. Cerebri Media (MCA) und A. Cerebri Anterior (ACA), Aufsuchen der Stelle mit der maximalen Flussgeschwindigkeit entlang der MCA, Dokumentation von TAMMX von MCA und ACA
- Schallkopf wenig nach kaudal kippen, Darstellung der distalen A. Carotis Interna (ICA), Dokumentation TAMMX
- Darstellung A. Cerebri Posterior (PCA), Dokumentation TAMMX
- Zugangsweg nuchal: Darstellung und Dokumentation TAMMX der A. Basilaris

TCD bei SCD


TCD
Normal
TAMMx < 170cm/s
Grenzwertig
TAMMx 170 - 199cm/s
Pathologisch
TAMMx ≥ 200cm/s
Kurzfristige Kontrolle (2-3 Wochen)
Kontrolle 1 Jahr
Kontrolle 3 Monate
Beginn Transfusionsprogramm Ziel: HbS < 30%

TCD bei SCD

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Discontinuing Prophylactic Transfusions Used to Prevent Stroke in Sickle Cell Disease

RESULTS

The study was stopped after 79 children of a planned enrollment of 100 underwent randomization. Among the 41 children in the transfusion-halted group, high-risk Doppler results developed in 14 and stroke in 2 others within a mean (±SD) of 4.5±2.6 months (range, 2.1 to 10.1) of the last transfusion. Neither of these events of the composite end point occurred in the 38 children who continued to receive transfusions. The average of the last two transcranial Doppler results before transfusion was started was the only predictor of the composite end point (P=0.05).

CONCLUSIONS

Discontinuation of transfusion for the prevention of stroke in children with sickle cell disease results in a high rate of reversion to abnormal blood-flow velocities on Doppler studies and stroke. (ClinicalTrials.gov number, NCT00006182.)

TCD bei SCD

Stroke With Transfusions Changing to Hydroxyurea (SWiTCH)

Russell E. Ware[1] and Ronald W. Helms,[2] for the SWiTCH Investigators

[1]Baylor College of Medicine, Houston, TX; and [2]Rho Inc, Chapel Hill, NC

Stroke is a devastating complication of sickle cell anemia (SCA) with high recurrence if untreated. Chronic transfusions reduce recurrent strokes but have associated morbidities including iron overload. Stroke With Transfusions Changing to Hydroxyurea (SWITCH) was a multicenter phase 3 randomized trial comparing standard treatment (transfusions/chelation) to alternative treatment (hydroxyurea/phlebotomy) for children with SCA, stroke, and iron overload. SWITCH was a noninferiority trial with a composite primary end point, allowing an increased stroke risk but requiring superiority for removing iron. Subjects on standard treatment received monthly transfusions plus daily deferasirox iron chelation. Subjects on alternative treatment received hydroxyurea plus overlap transfusions during dose escalation to maximum tolerated dose (MTD), followed by monthly phlebotomy. Subjects on standard treatment (N = 66) maintained 30% sickle hemoglobin (HbS) and tolerated deferasirox at 28.2 ± 6.0 mg/kg/d. Subjects on alternative treatment (N = 67) initiated hydroxyurea and 60 (90%) reached MTD at 26.2 ± 4.9 mg/kg/d with 29.1% ± 6.7% fetal hemoglobin (HbF). Adjudication documented no strokes on transfusions/chelation but 7 (10%) on hydroxyurea/phlebotomy, still within the noninferiority stroke margin. The National Heart, Lung, and Blood Institute closed SWITCH after interim analysis revealed equivalent liver iron content, indicating futility for the composite primary end point. Transfusions and chelation remain a better way to manage children with SCA, stroke, and iron overload. This clinical trial was registered at ClinicalTrials.gov NCT00122980.

(*Blood*. 2012;119(17):3925-3932)

TCD bei SCD

Hydroxyurea therapy lowers transcranial Doppler flow velocities in children with sickle cell anemia

Sherri A. Zimmerman,[1] William H. Schultz,[2] Shelly Burgett,[1] Nicole A. Mortier,[2] and Russell E. Ware[2]

[1]Duke Pediatric Sickle Cell Program and Division of Pediatric Hematology/Oncology, Duke University Medical Center, Durham, NC; [2]Department of Hematology, St Jude Children's Research Hospital, Memphis, TN

Hydroxyurea has hematologic and clinical efficacy in sickle cell anemia (SCA), but its effects on transcranial Doppler (TCD) flow velocities remain undefined. Fifty-nine children initiating hydroxyurea therapy for clinical severity had pretreatment baseline TCD measurements; 37 with increased flow velocities (≥ 140 cm/s) were then enrolled in an institutional review board (IRB)–approved prospective phase 2 trial with TCD velocities measured at maximum tolerated dose (MTD) and one year later. At hydroxyurea MTD (mean ± 1 SD = 27.9 ± 2.7 mg/kg per day), significant decreases were observed in the right middle cerebral artery (MCA) (166 ± 27 cm/s to 135 ± 27 cm/s, $P < .001$) and left (MCA) (168 ± 26 cm/s to 142 ± 27 cm/s, $P < .001$) velocities. The magnitude of TCD velocity decline was significantly correlated with the maximal baseline TCD value. At hydroxyurea MTD, 14 of 15 children with conditional baseline TCD values improved, while 5 of 6 with abnormal TCD velocities whose families refused transfusions became less than 200 cm/s. TCD changes were sustained at follow-up. These prospective data indicate that hydroxyurea can significantly decrease elevated TCD flow velocities, often into the normal range. A multicenter trial is warranted to determine the efficacy of hydroxyurea for the management of increased TCD values, and ultimately for primary stroke prevention in children with SCA.

(Blood. 2007;110:1043-1047)

TCD bei SCD

For Immediate Release: Wednesday, November 19, 2014

NIH ends Transcranial Doppler (TCD) with Transfusions Changing to Hydroxyurea (TWiTCH) clinical trial due to early results

The TWiTCH study sought to determine whether giving daily doses of hydroxyurea (currently the only FDA-approved drug for sickle cell disease) lowers the TCD blood velocity in children with sickle cell disease (SCD) to a similar degree as blood transfusions. Children with sickle cell disease who are at a higher risk for stroke are identified by measuring the velocity of blood flow to the brain by TCD ultrasound studies. Children with the highest TCD velocities have a greater risk of strokes. The early review showed that hydroxyurea reduces TCD blood velocities to a similar degree as blood transfusions.

The results of this study show that hydroxyurea is not inferior to (that is, no worse than) regular blood transfusions in lowering TCD velocities in children with sickle cell disease who are at high risk for stroke.

Ulmer Erfahrungen

- 25 Patienten untersucht seit Sommer 2010
- Darunter 16 Patienten mit unauffälligem Befund (1-5 Untersuchungen / Patient)
- 6 Patienten mit grenzwertigem Befund, teilweise in der Kontrolle nach 3 Monaten unauffällig, teilweise über längeren Zeitraum hinweg
- 3 Patienten mit pathologischem Befund

Ulmer Erfahrungen

Patient 1:

- Homozygote SCD (ED mit 4 Monaten)
- Rezidivierend Milzsequestrationen, Splenektomie mit 11 Monaten
- Im Alter von 2 7/12 Jahren schlaffe Parese rechter Arm distal betont
- Kernspintomographie: Infarkt MCA links
- Sofortige partielle Austauschtransfusion
- Beginn chronisches Transfusionsprogramm
- TCD: nivelliertes poststenotisches Flusssignal der MCA links, pathologischer Fluss der ACA rechts
- Neurologische Rehabilitation, deutliche Besserung der Halbseitensymptomatik
- HLA-Typisierung, Fremdspendersuche
- Unter Transfusionsprogramm Normalisierung des Flusses der ACA rechts

Ulmer Erfahrungen

Patient 2:

- Älterer Bruder von Patient 1
- Homozygote SCD
- Rezidivierend Thoraxsyndrom im Alter von 1-2 Jahren
- Alter von 5 4/12 Jahren: TCD mit pathologischem Fluss der ACA rechts, klinisch kein Hinweis auf Infarkt
- Beginn chronisches Transfusionsprogramm
- Unter Transfusionsprogramm Normalisierung des Flusses der ACA rechts

Zusammenfassung

- Akuter ZNS-Infarkt: Indikation für allogene Stammzelltransplantation
- Reduktion des Risikos für ein Infarktrezidiv: lebenslanges Transfusionsprogramm
- Reduktion des Risikos für einen Infarkt bei Kindern mit pathologischem TCD-Ergebnis: Transfusionsprogramm mindestens bis ins Erwachsenenalter
- Beginn Transfusionsbehandlung bei zwei innerhalb weniger Wochen unabhängig voneinander durchgeführten TCD-Untersuchungen mit pathologischem Ergebnis ohne Vorliegen einer schwergradigen Anämie (Hb-Gehalt entspricht steady state des Patienten)
- Alternative (ohne vorangegangenen Infarkt): Hydroxycarbamid
- Ggfs. Kombination Transfusionsprogramm und Hydroxycarbamid bei Progress

Vielen Dank für Ihre Aufmerksamkeit

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