

TCD ULTRASOUND IN BABIES WITH SICKLE CELL ANEMIA INCLUDING A REVIEW OF THE BABY HUG PROGRAM

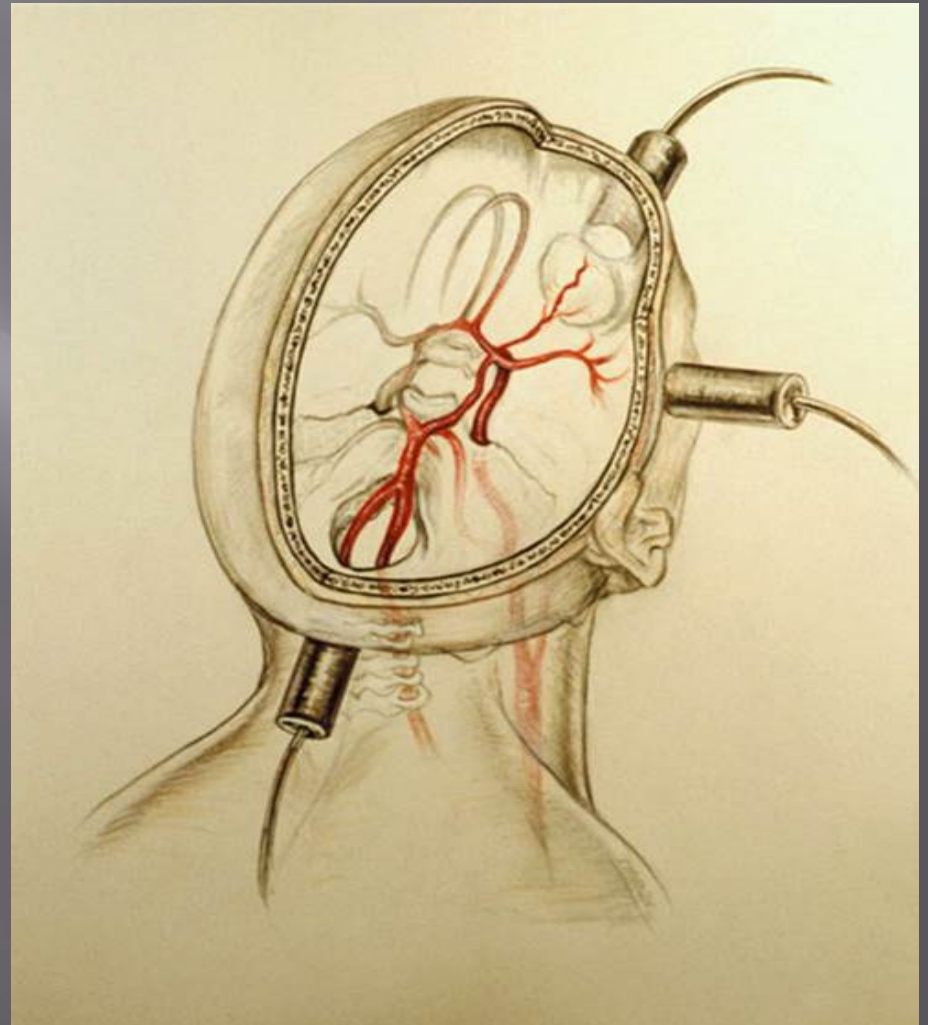
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THANK YOU!



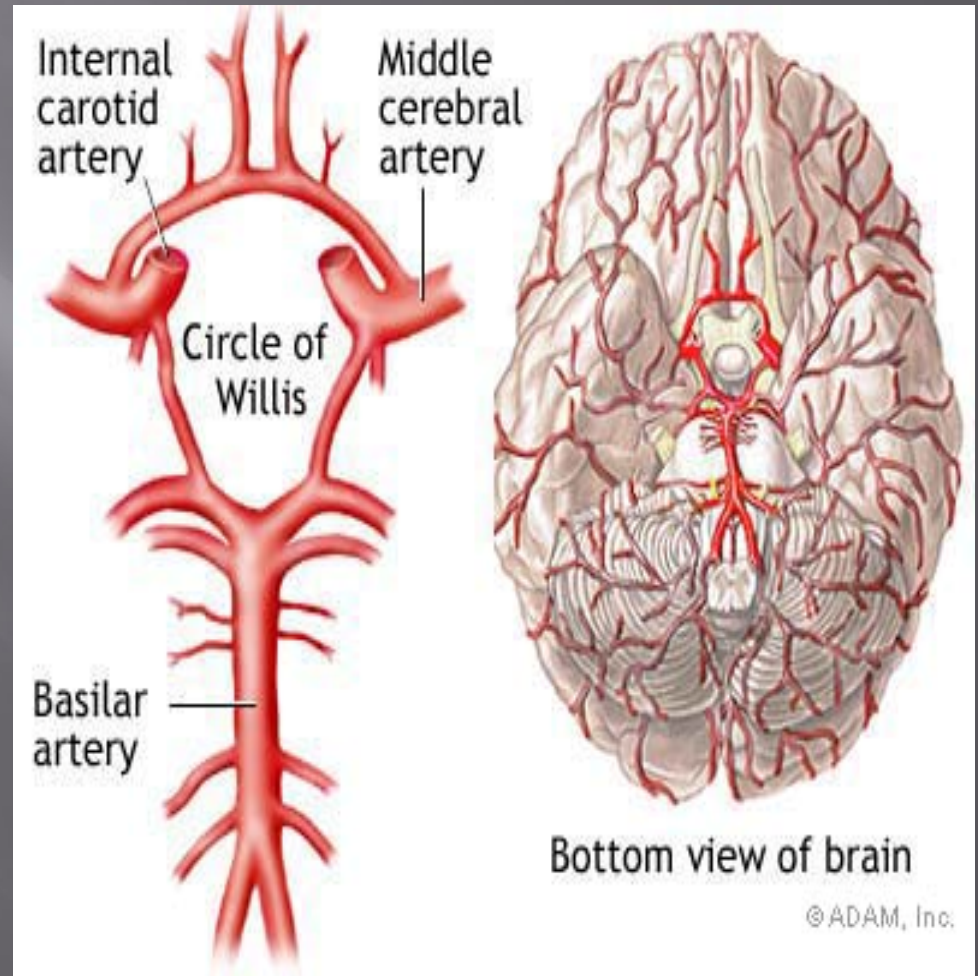
Transcranial Doppler Ultrasound

- ▣ Transcranial Doppler ultrasound (TCD) is a non-invasive technique
- ▣ Used to evaluate blood flow in the major intracranial arteries of the Circle of Willis



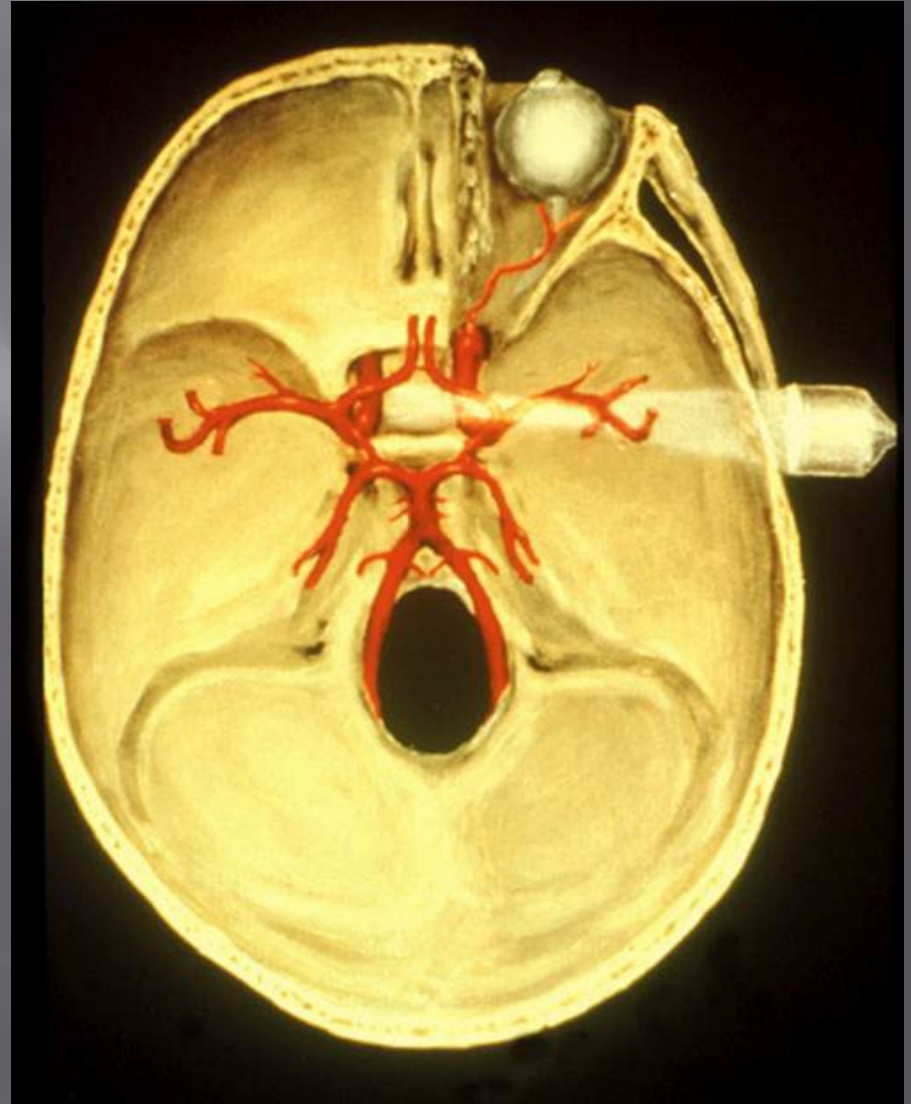
Circle of Willis

- ❑ Circle of Willis is the vascular network that supplies blood to the brain
- ❑ Joins the two internal carotid systems and the vertebral-basilar circulation



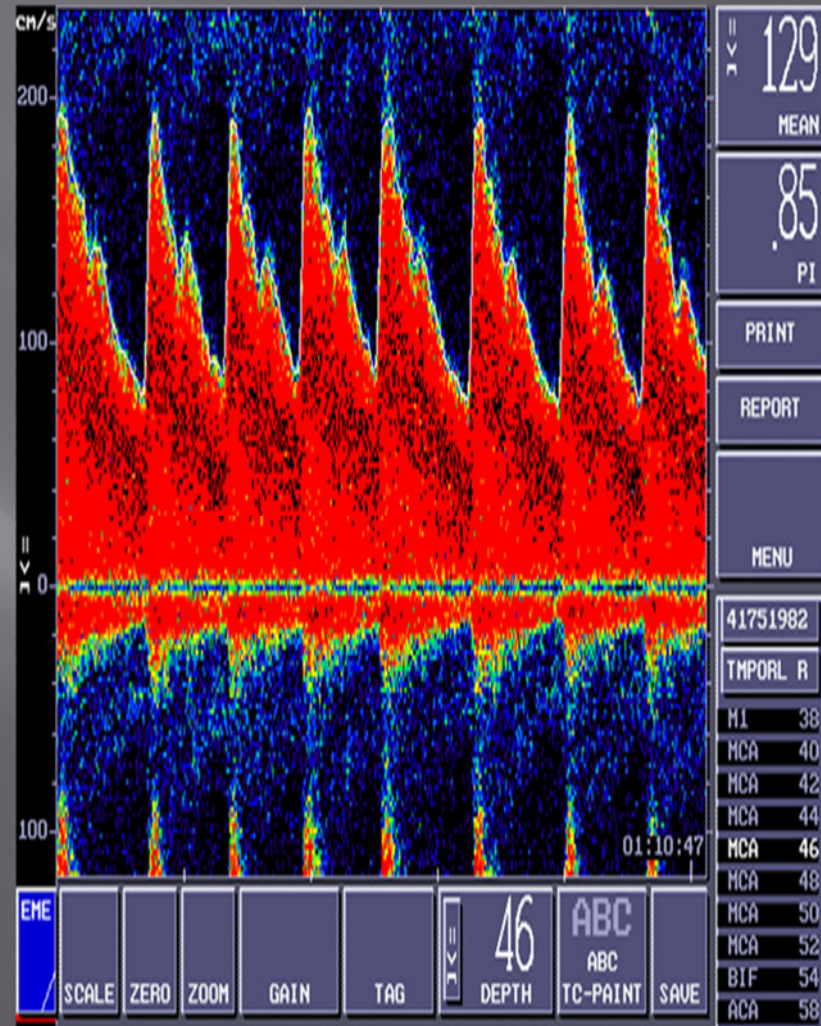
TCD BASICS

- ▣ TCD was introduced by Rune Aaslid, PhD in 1982
- ▣ Uses a 2-MHz pulsed Doppler ultrasound to measure blood flow velocity, not blood flow volume



TCD BASICS

- TCD is a non-imaging exam
- There is no B-mode image to identify the vessel and its location



TCD BACKGROUND

- Between 1988 and 1992, Dr. Robert Adams and team at the Medical College of Georgia worked together to validate TCD as a tool to measure the velocity of cerebral blood flow in children and young adults (ages 3-18) being followed for sickle cell disease and identify those at highest risk for stroke

TCD BACKGROUND



- ▣ Subsequently, 1995-1997, TCD screening was used in the Stroke Prevention Trial in Sickle Cell Anemia (STOP). STOP was a randomized trial that confirmed the prior reports of using TCD as a predictor of arterial ischemic stroke (AIS) in children with SC (2-16 yrs. of age) and showed transfusion to dramatically decrease the risk of stroke

TCD BACKGROUND

- ▣ Based on compelling results of the STOP study, The National Heart, Lung, Blood Institute (NHLBI) recommended TCD for SCD children, beginning at age 2 years, with no prior stroke



TCD IN BABIES

- ▣ While TCD became widely recognized as a way of predicting stroke risk in older children with SCD, TCD had not yet been adequately studied in children under age 2 years



FEASIBILITY OF TCD IN BABIES

In 2002, a pilot study at the Medical College of Georgia was conducted to determine the feasibility of obtaining adequate TCD in babies with SCD

As a result, TCD was proven achievable

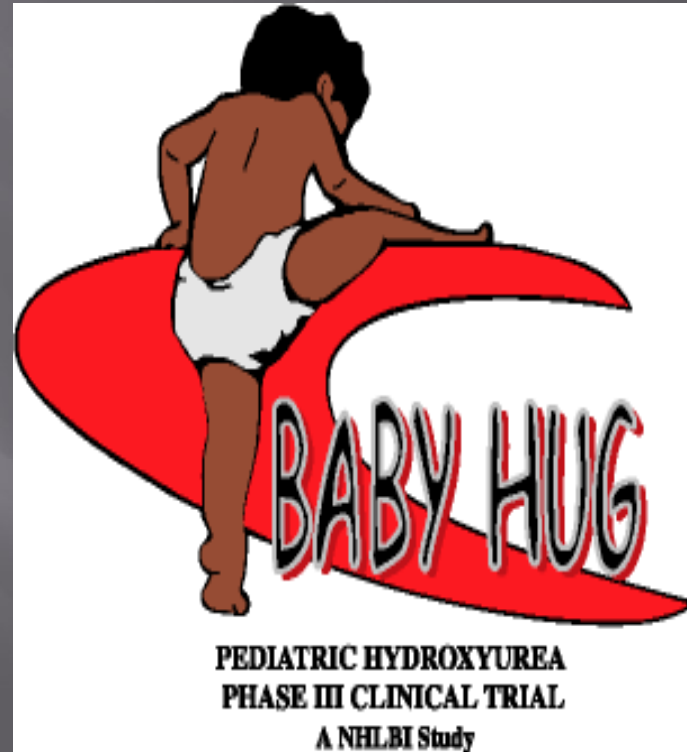
Attempted in 27 babies

4 failed attempts

23 adequate exams

BABY HUG TRIAL

- Between October 2003 and September 2009, TCD was a secondary study endpoint in a new trial focusing on children 2 years and younger
- This trial was undertaken by 13 centers in the USA





BABY HUG TRIAL

The Pediatric Hydroxyurea Phase 3 Clinical Trial (BABY HUG)

- BABY HUG was a multicenter, double-blinded randomized comparison of daily oral hydroxyurea (HU; 20 mg/kg per day) versus placebo in infants with sickle cell anemia (SCA; HbSS or S β^0 thalassemia) sponsored by the NHLBI and National Institute of Child Health and Human Development (NICHD)

BABY HUG TRIAL

PURPOSE:

- What is the best age range when considering HU therapy for the prevention of organ damage?
- Should HU be reserved only for patients with severe disease or might less severely affected infants benefit as well?
- Can HU help prevent the chronic end organ damage in sickle cell disease that begins in early life?

PRIMARY ENDPOINT

- The primary aim of the trial was to determine whether daily hydroxyurea would reduce spleen and renal damage by $\geq 50\%$

METHODS

Enrolled BABY HUG Subjects:

- Confirmed diagnosis of Hb SS or Hb S β^0
- 9-18 months of age (screening began at age 7 months)
- No history of stroke
- Not receiving chronic blood transfusion
- Were not chosen for clinical severity



SECONDARY ENDPOINT

- TCD performed as a secondary endpoint
- Compare prevalence of high-risk TCD between two groups of children treated for 2 years with HU or placebo to estimate the likelihood that HU affects stroke risk
- Compare post-treatment TCD between treatment groups to test whether HU lowers time averaged maximum mean (TAMM) velocity in the middle cerebral artery (MCA) and other arteries

TCD METHODS

- TCD schedule in BABY HUG
 - Baseline
 - 12 months
 - 24 months

TCD METHODS

- Nicolet Companion TCD machine with a 2 MHz Doppler probe was used
- BABY HUG certified examiners performed the TCD exams
- Effort to complete the exam within 30-45 minutes
- No sedation was used

TCD METHODS



The STOP TCD exam protocol was used



With the following exceptions:

- The sample volume was decreased to 4mm to accommodate the smaller head sizes
- The Basilar artery was not insonated

TCD METHODS

Major intracranial cerebral vessels were insonated through the thinnest part of the temporal bone using the Transtemporal approach



TCD METHODS

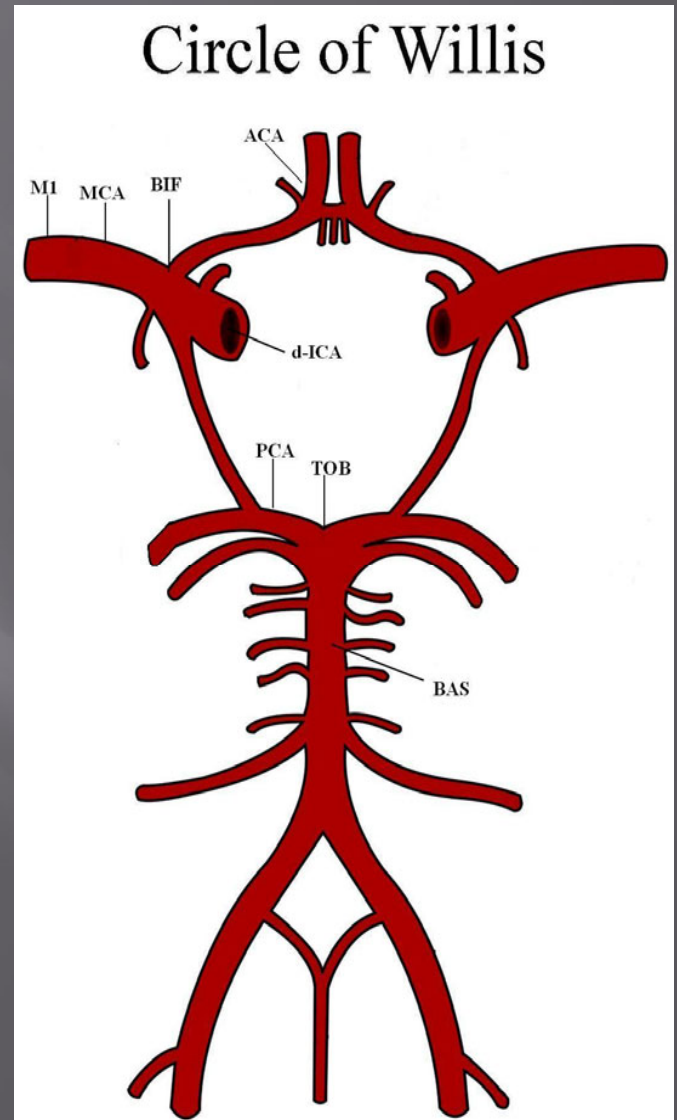
Arterial segments on each temporal side were insonated

- Labeled:
- M1 (most distal portion of **M**iddle **C**erebral **A**rtery)
- MCA (mid portion of **M**iddle **C**erebral **A**rtery)
- BIF (termination of ICA, **B**ifurcates **M**CA/**A**CA)
- d-ICA (**D**istal **I**nternal **C**arotid **A**rtery)
- ACA (**A**nterior **C**erebral **A**rtery)
- PCA (**P**osterior **C**erebral **A**rtery)
- TOB (**T**op **o**f **B**asilar Artery)

TCD METHODS

Right and Left Temporal Sides

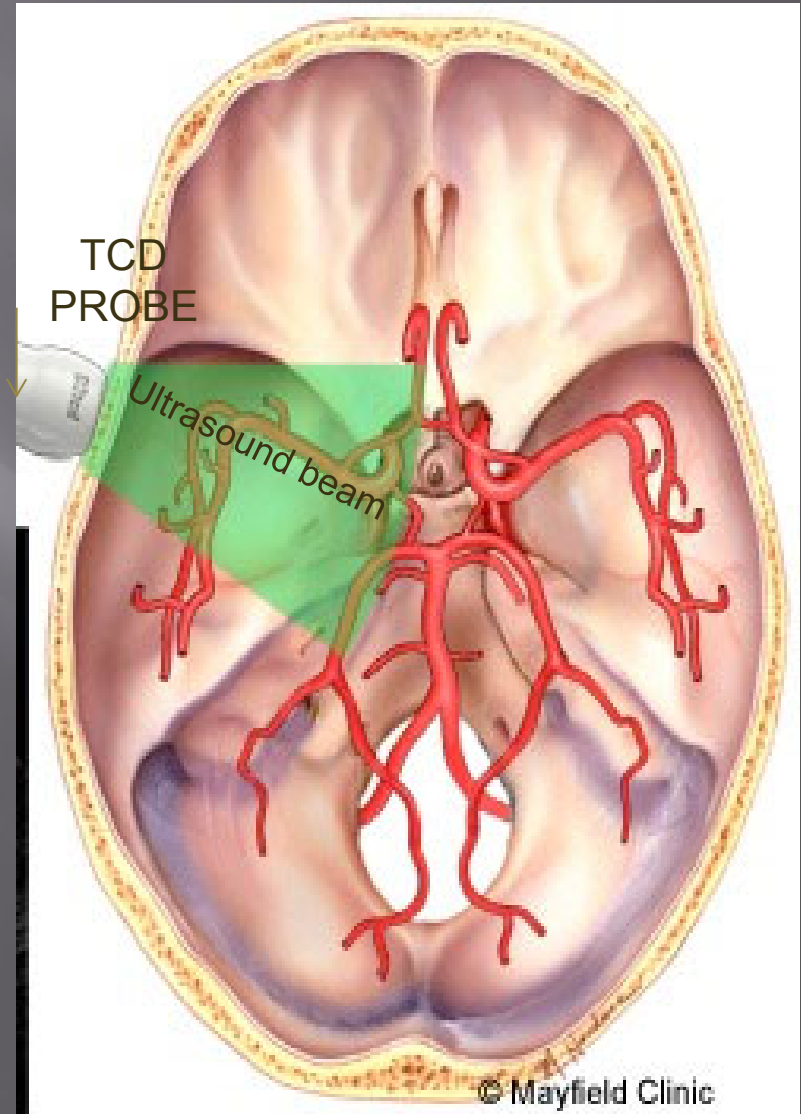
- M1
- MCA
- BIF
- d-ICA
- ACA
- PCA
- TOB



TCD METHODS

IDENTIFYING A VESSEL:

- Find BEST Window
- Direction of blood flow
- Depth of the sample volume
- Angle of the probe
- Spatial relationship of vessels
- Audio quality



TCD METHODS

LISTEN

Fundamental to the performance of a high quality TCD exam is a learned ability to listen for distinguishable audible Doppler signals with the highest pitch and strength



BABY TCD

- ▣ Prior to beginning the TCD exam AVOID venipuncture or any other stressful procedures for baby

TCD EXAM

- Describe the TCD equipment and the exam to parents



TCD EXAM

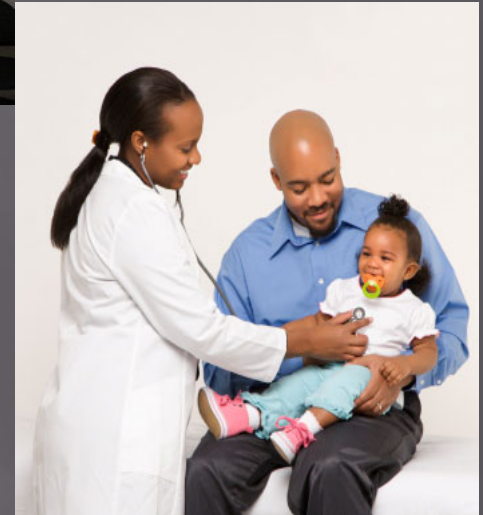
- ▣ Answer any parental questions regarding TCD
- ▣ Offer thoughtful and personal attention
- ▣ Each family is unique and special



BEFORE BEGINNING TCD

Baby Whisperer

- ▣ Adjust the bright lights to soft and dim
- ▣ Expressively connect with baby...SMILE
- ▣ Speak in a quiet tone to reduce baby's stress



DURING TCD EXAM

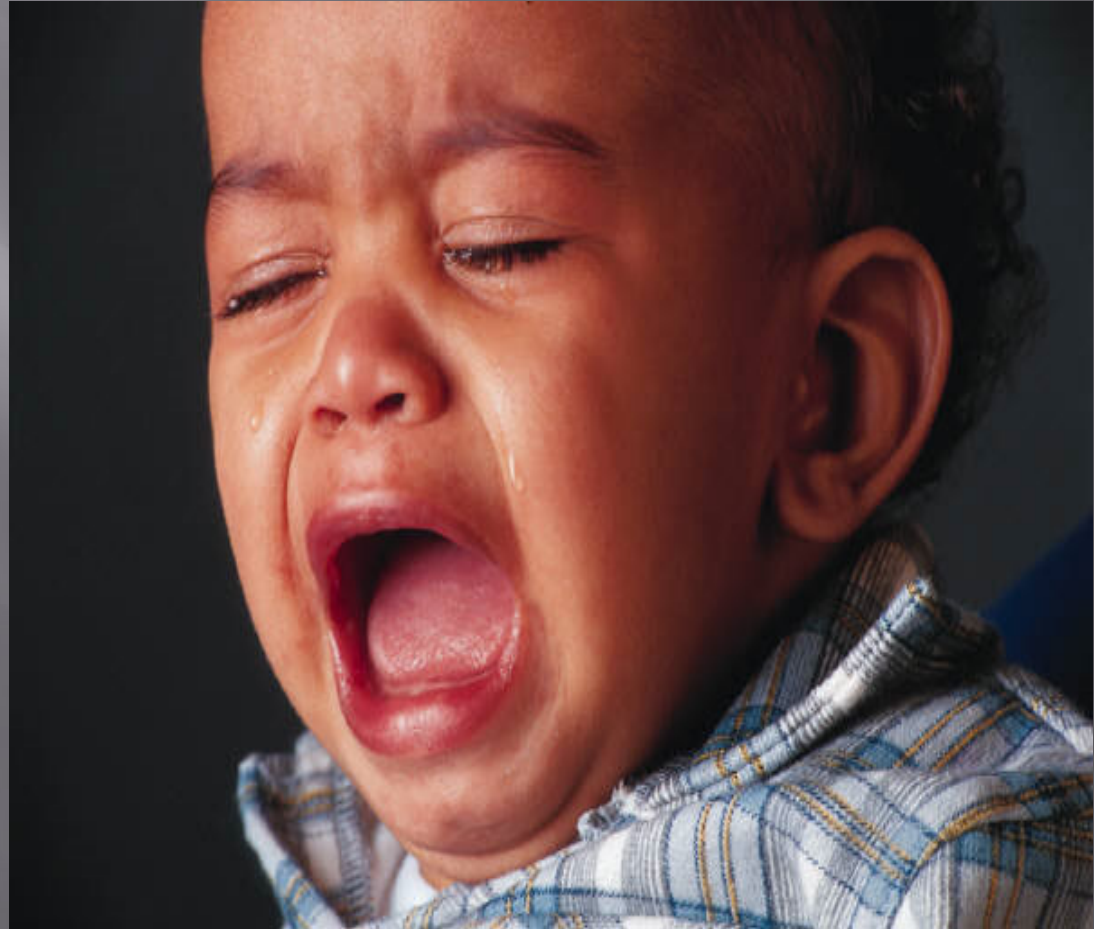
- ▣ Encourage parental support and involvement during the TCD exam
- ▣ Children need reassurance that only their parents can provide



BABY TCD

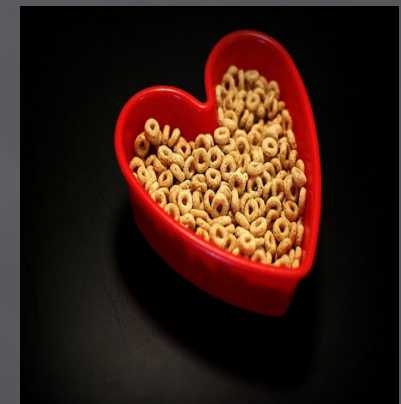
UH-OH!!!

WHAT NOW?



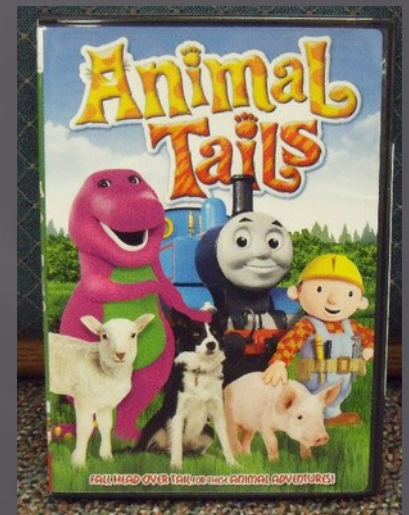
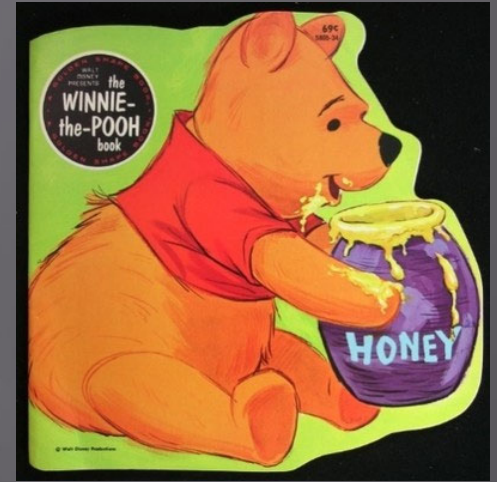
COMFORTS

- ▣ Offer soothing comforts to baby



DISTRACTIONS

- Soft cuddly toys
- Books
- Cell phones
- Movies (careful not to drown out distinct ultrasounds)



PARENTAL SUPPORT

- ▣ Ask parent for help and support
- ▣ If baby is uncooperative, position baby in mother's arms
- ▣ Stand behind baby, adjust TCD probe accordingly



BABY TCD



- ▣ **Develop personal strategy for coping when things do not go as planned**
- ▣ **Walk away from doing TCD for a moment to avoid becoming anxious about completing the exam**

BABY TCD

- ▣ Give baby and parents a short break
- ▣ Time permitting, allow baby to take a brief nap
- ▣ Attempt again later



BABY TCD

THE TEMPTATION TO
QUIT WILL BE
GREATEST JUST
BEFORE YOU ARE
ABOUT TO SUCCEED.

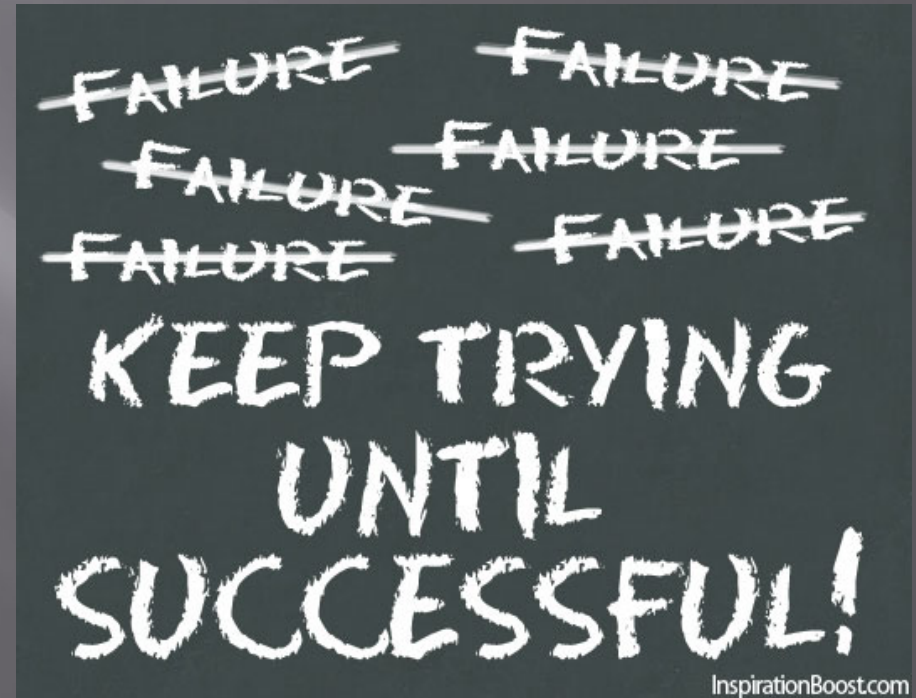
CHINESE PROVERB

ZERODEAN.COM



TCD ATTEMPTS

- ▣ If the first attempt at obtaining TCD exam is a failure, make another effort at the child's next regularly scheduled appointment
- ▣ The next try may be less stressful and a complete success

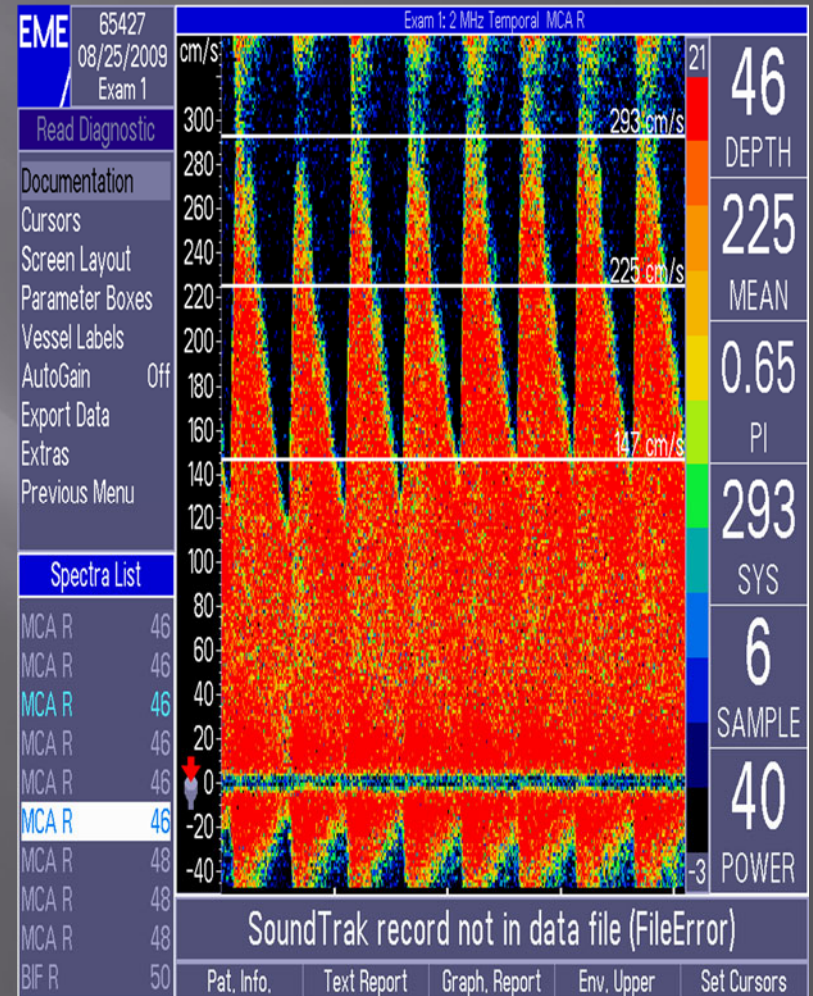


BABY HUG METHODS

- The STOP study reading protocol was used to determine the Time Average Maximum Mean (TAMM) velocity
- TCD exam result is based on the TAMM

TCD METHODS

- ▣ The highest TAMM velocity from the MCA or distal ICA velocity on either side was identified



TCD METHODS

- For TCD to be classified as Abnormal, a velocity ≥ 200 cm/sec had to be identified in at least one of the following segments:
- M1, MCA, BIF of dICA

TCD METHODS

Interpretation:	Velocities:	Stroke Risk Level:
Normal	<170cm/sec	Low
Conditional	170-199cm/sec	Moderate
Abnormal	≥200cm/sec	High
Inadequate	Unreadable	Unknown

- TCD exams were reviewed at the Medical College of Georgia after blinding to treatment (HU or placebo)
- If TCD result was abnormal the subject was considered to be at high risk and was not eligible for enrollment in BABY HUG

TCD RESULTS

- The increase in TAMM maximum TCD velocity, from baseline to exit, was lower in the hydroxyurea group than in the placebo group (20cm/sec vs. 32 cm/sec)

BABY HUG RESULTS

- 193 infants with HbSS (n=187) or S β^0 thalassemia (n=6), mean age 13.6 months, were randomized and 192 began study medication
- At baseline, 52 (54%) of 96 children in the hydroxyurea group and 49 (51%) of 97 children in the placebo group were clinically asymptomatic
- 167 (86%) completed the full study

BABY HUG RESULTS

Baseline characteristics of the study population reported no significant differences in age, sex, genotype, clinical severity of sickle cell anemia, lab values or physical findings between the two groups

BABY HUG RESULTS

- ▣ No significant difference between hydroxyurea and placebo groups for either of the primary endpoints were recorded

BABY HUG RESULTS

- Overall, there were 2560 AEs and 107 SAEs reported during a total of 374 patient-years of on-study observation

BABY HUG RESULTS

- Hydroxyurea significantly reduced the frequency of painful events, acute chest syndrome, and associated transfusions and hospitalizations, without significant hydroxyurea-related AEs

BABY HUG RESULTS

- Fifty-four percent of children in the hydroxyurea group were clinically asymptomatic at enrollment and also had significant reductions in sickle-cell related events
- Beneficial effects of hydroxyurea occur in both asymptomatic and symptomatic young children with SCA

BABY HUG RESULTS

- The Baby Hug study is, to our knowledge, the first randomized, double-blind prospective pediatric trial to investigate the effect of HU in very young children with SCA
- Subjects differed from those in other trials in two important ways:
 - they were very young and
 - eligible irrespective of whether they had severe clinical course of disease.

RESULTS

On the basis of safety and efficacy data from the BABY HUG trial, HU can now be considered for all very young children with sickle cell anemia

BABY HUG FOLLOW UP

- ▣ An open-label follow-up study of this cohort that allows dose escalation is underway
- ▣ Of the 179 patients who completed at least 18 months of follow-up in the BABY HUG trial, 91% are enrolled in the follow-up study

BABY HUG FOLLOW UP

- TCD, as well as a steady collection of clinical events and safety data, are being performed in the current BABY HUG Follow-up Study that has been extended through 2016

TCD

- ▣ TCD is now being performed internationally in children with SCD to screen and identify those at greatest risk for ischemic stroke



TCD IN BABIES AND CHILDREN

HONOR AND PRIVILEGE



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