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Can peak systolic velocities be used for prediction of stroke in sickle cell anemia?

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Abstract Background and purpose: Ischemic stroke occurs in at least 11% of patients with homozygous sickle cell anemia (SCD) by the time they turn 20 years old. High risk associated with distal intracranial internal carotid (ICA) and proximal middle cerebral artery (MCA) stenosis can be detected by transcranial Doppler (TCD). TCD screening offers the possibility of reducing the risk of first stroke significantly based on a paradigm tested and proven to be effective in a stroke prevention trial in sickle cell anemia (STOP). Children with high flow velocity in the ICA and MCA of 200 cm/s time average mean of the maximum (TAMM) or higher had a 10% per year risk of first stroke that was reduced to <1% with regular red cell transfusion (reduction of hemoglobin S <30%). The clinical application of the STOP results could be enhanced if criteria for treatment could be found that are based on peak systolic velocity (PSV), the measure more commonly used in vascular ultrasound practice.

Objective: To compare PSV and end diastolic velocity (EDV) with TAMM for prediction of stroke and to derive PSV cutpoints for STOP protocol definitions of conditional and abnormal TCD. Using the STOP TCD and stroke outcome data to compare PSV and TAMM in terms of stroke prediction, PSV cutpoints comparable to those based

on TAMM and used in STOP were derived. Because of their familiarity to the vascular ultrasound community, PSV cutpoints should be an important alternative to TAMM and may increase availability of screening and risk stratification for children with this disease.

Materials and methods: Data from 1,937 baseline TCD studies from STOP were correlated with stroke outcome in those not treated with transfusion. Stroke prediction was assessed with survival analysis using TAMM, PSV and EDV as continuous variables individually and then pair-wise in the same model, which contained 53 stroke events.

Results: PSV and EDV were highly correlated to the TAMM velocity ($r=0.94$). The multivariate model for prediction indicated that TAMM velocity was a better predictor than EDV, and PSV and TAMM were approximately equivalent. PSV cutpoints defining the two relevant STOP risk categories—"conditional," which should lead to increased TCD surveillance, and "abnormal," which should lead to strong consideration for treatment according to STOP—were derived taking into consideration known differences in measurements between the dedicated Doppler systems (TCD) used in STOP and the transcranial Doppler imaging (TCDI) systems commonly used in clinical practice. The recommended PSV

cutpoint for conditional TCD is 200 cm/s, and for abnormal TCD triggering consideration for treatment is 250 cm/s.

Conclusion: Assuming TCDI equipment is used and the STOP protocol is applied, a PSV cutpoint of 200 cm/s is recommended as the threshold for increased TCD

surveillance (comparable to a TCD TAMM of 170 cm/s in STOP); a PSV of 250 cm/s is recommended as the cutpoint at which, if confirmed in a second examination, chronic transfusion should be considered.

Assuming the STOP scanning protocol is used, PSV is at least as good as TAMM and can be used to select

children with SCD for treatment or increased surveillance to prevent first stroke.

Keywords Sickle cell disease · Stroke · Transcranial Doppler · Peak systolic velocity

Introduction

The stroke prevention trial in sickle cell anemia (STOP) used transcranial Doppler (TCD) to identify and treat those children with sickle cell anemia (SCD) at the highest risk of stroke [1–7]. The STOP trial showed that marked reduction of first stroke is possible with TCD screening and prophylactic blood transfusion, and the National Heart Lung and Blood Institute (NHLBI) and the American Stroke Association have recommended TCD screening for all children with sickle cell disease who are 2–16 years of age [8]. Risk stratification was based on time averaged mean of the maximum (TAMM) [9] velocities, a measure less commonly used than peak systolic (PSV) in clinical ultrasound practice [10]. TAMM was used in all of the original TCD-based publications, and most clinical experience in TCD has used TAMM velocities. In contrast, when Doppler ultrasound exams are reported for extracranial arterial studies, the most commonly used velocities are PSV and end diastolic (EDV). We report here an attempt to develop correlations for PSV and EDV with the TAMM velocities used in STOP. To make the STOP data more useful in clinical practice, the stroke prediction data from STOP were used to compare PSV and EDV to TAMM in terms of stroke prediction and to derive PSV measures of stroke risk comparable to the TAMM cutpoints of 170 cm/s for “conditional TCD” (triggering increased surveillance) and 200 cm/s for “abnormal or high risk TCD” (triggering prophylactic chronic transfusion) [11–13].

Materials and methods

The design of the STOP trial is described in detail elsewhere [14]. Briefly, a large cohort of children aged 2–16 years with confirmed hemoglobin SS or $S\beta^0$ thalassemia were screened with TCD. Children at high risk of stroke based on previously published velocity criteria [3, 4] were randomly assigned to receive standard medical care or to get regular blood transfusions designed to keep sickle hemoglobin below 30% [15]. Children with a

prior clinical stroke were excluded. Recruitment and TCD screening for STOP occurred from February 1995 to November 1996, and stroke surveillance continued until June 2000. All randomized patients except one were followed for stroke until June 2000, and we attempted to make yearly contact with all children who had been screened with TCD to assess stroke and vital status. From November 1996 until November 1999, TCD screening was offered as an ancillary study to patients not enrolled in the main trial in order to examine rates of conversion from low-risk to high-risk states over time. All STOP centers participated in this ancillary study and used TCD methods comparable to those of the initial TCD screen. In the TCD ancillary study, investigators were encouraged to enroll and restudy younger (SCD) patients (we assumed that these children would be more likely to change TCD risk category) and to restudy those with “conditional” TCD during initial screening (see below). However, any screened patient and any new patient who met original STOP screening criteria were also eligible for the ancillary study [16]. Follow-up was most complete for those who participated in the randomized part of the study (129 of 130 were followed until end of study), but the TCD-screened-only group was also monitored for stroke for almost as long. The mean follow-up of these patients was 50 ± 16 months, and 75% of the sample had 60 months of follow-up or more.

Between 1995 and 1999 the STOP study performed a TCD examination on 2325 children. Of these, 267 had no further follow-up. From the remaining 2,058 patients, 130 at high risk were randomized to the trial itself and followed for stroke. Those screened but not randomized were also followed for the occurrence of stroke. The performance of TCD was standardized and is described in detail elsewhere. A dedicated 2-MHz pulsed Doppler (“non-imaging”) machine (Nicolet TC-2000; Madison, Wis.) was used, and studies were sent on diskette to the data center (New England Research Institutes, Boston, Mass.) for archiving and blinding, then sent electronically to the Medical College of Georgia in Augusta for central reading. The TCD examiners recorded spectra from a maximum of 13 arterial segments.

Readers classified each study into one of four mutually exclusive categories: normal, conditional, abnormal, and inadequate, based on highest TAMM on either side as follows: “normal” when all velocities were ≤ 170 cm/s; “conditional” when velocities were ≥ 170 but ≤ 200 cm/s; “abnormal” when either the internal carotid artery (ICA) or middle cerebral artery (MCA) on either side met or exceeded the 200 cm/s cutpoint; “inadequate” when studies lacked sufficient data for classification. Although only TAMM was used in STOP, PSV and EDV from each segment were recorded at the time of centralized reading. After inspection of the recorded spectra from all depth settings, the readers placed a cursor to read the three velocities (TAMM, PSV, EDV) from the most representative TCD spectra for the arterial segments of interest, sampling at least three cardiac cycles for measurement at each segment. Cursor placement prompted the software to record the velocities and to compute and record the pulsatility (PSV-DV/TAMM) and resistivity (PSV-DV/PSV) indices (PI and RI) at that segment.

Determination of stroke The method of stroke adjudication depended on whether a child was in the randomized or screened-only group. In the first case, focal symptoms consistent with cerebral infarction or ICH were required unless the presentation suggested subarachnoid hemorrhage. Post-event neuroimaging, usually MRI, was used to confirm clinical presentation and exam findings. A panel of two neurologists who were blinded to treatment status independently adjudicated each case as to whether an event was a stroke; a third neurologist was available in cases of disagreement. Adjudicators had access to all neuroimaging studies (films) performed in STOP on that patient. Only confirmed strokes taking place during the defined period of observation in STOP (1995–2000) are considered in this report. In the second group a similar process was applied, except that blinded adjudicators examined copies of the hospital records and neuroimaging (after removal of patient names) test results read by local center radiologists. In this group, diagnosis was based on history and examination (all cases) and the official reports of confirmatory tests: MR and CT (50%), MR (33%), CT (15%) or autopsy (2%).

Data analysis

Data from the baseline TCD examination were analyzed with respect to stroke outcome. Of the 2,058 children with follow-up data, 121 were excluded because their initial TCD was inadequate (no TAMM was recorded to which a PSV or EDV could be linked), leaving 1937 children (83% of those who had baseline TCD).

Descriptive statistics in relation to TAMM velocity were generated for the PSV and EDV at the segment where maximal TAMM was recorded and on which the categorical risk determination (normal, conditional or abnormal) was based as were over all qualifying segments. Data were censored at the point of initiation of chronic transfusion instituted for any reason. Using survival analysis, TAMM, PSV and EDV as continuous variables were compared in relationship to stroke risk using both forward selection and backward elimination methods. The three were then compared to one another by inclusion in a multivariate model. Descriptive statistics for PSV associated with the three STOP risk stratification categories were generated.

Results

Baseline TCD data from 1,937 children with SCD were analyzed. The highest PSV and EDV from the same arterial segment were correlated to the TAMM. There was considerable variability in the waveform as reflected by the PI and RI among patients in STOP, which affected the relationship between PSV and EDV to TAMM. The range for the PI was 0.28–1.78 with a median of 0.73, and the entire range for the RI was 0.22–0.81 with a median of 0.52.

Velocities from the same TCD were Pearson-correlated. Figures 1 and 2 show the regression of PSV and EDV against TAMM. PSV and EDV were both strongly correlated with TAMM ($r=0.94$ for PSV and 0.95 for EDV); PSV and EDV were also correlated ($r=0.84$).

There were 53 verified strokes in 53 children in the risk model used for this analysis. TAMM, PSV and EDV were highly associated with stroke ($P<0.001$) when examined independently. Regarding comparison among the three as predictors, the analysis gave some-

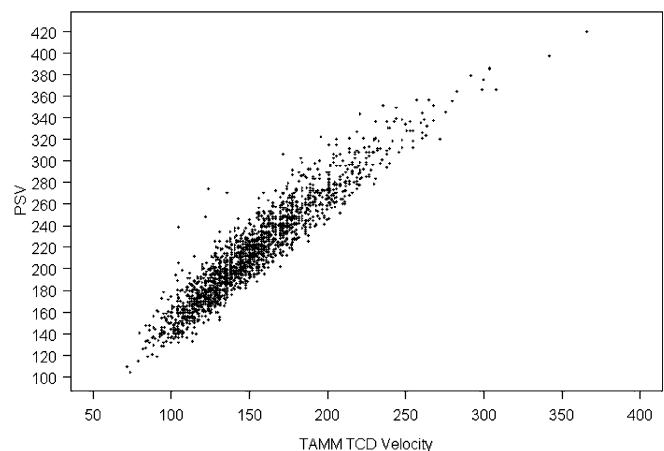


Fig. 1 Peak systolic velocity (PSV) vs TAMM TCD velocity

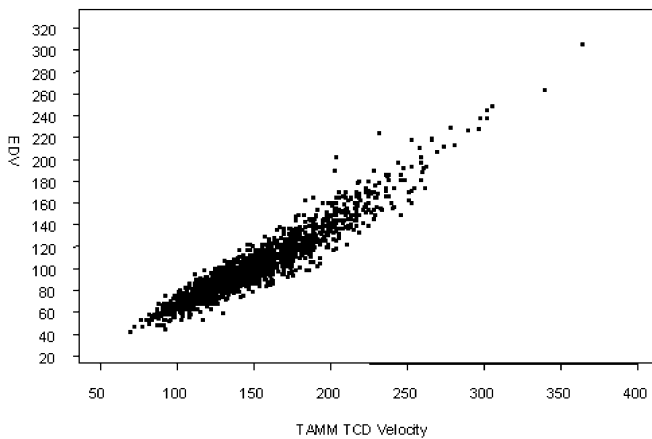


Fig. 2 End diastolic velocity (EDV) vs Tamm TCD velocity

what conflicting results: using forward selection methods, the model retained Tamm and rejected EDV and PSV; using backward elimination, the model selected PSV and rejected EDV and Tamm.

The maximum PSV and EDV in relation to Tamm from all examinations, and from 1358 examinations read in STOP (on the basis of Tamm) as normal, 373 classified as conditional, and 206 classified as abnormal are shown in Tables 1–4, respectively. The mean PSV of normal studies was 193 cm/s, from conditional studies it was 246 cm/s, and from abnormal TCD it was 298 cm/s. Because the waveform that determines the relationship between PSV, Tamm and EDV showed considerable variation in children with SCD, there was some overlap in the ranges for PSV and EDV in each STOP risk category defined by the Tamm.

Discussion

The STOP dataset with 53 stroke endpoints and 1,937 overall screened children provides the largest prospective

Table 1 Velocities from 1,937 TCD baseline examinations

	Velocity (cm/s, mean \pm SD)
PSV	214 \pm 45
Tamm	152 \pm 36
DV	104 \pm 29

Table 2 PSV and DV from 1,358 normal TCD examinations

	Velocity (cm/s)	
	Mean \pm SD	Range
PSV	192 \pm 28	104–300
Tamm	134 \pm 19	72–169
DV	90 \pm 15	45–141

Table 3 PSV and DV from 373 conditional TCD examinations

	Velocity (cm/sec)	
	Mean \pm SD	Range
PSV	246 \pm 23	165–322
Tamm	177 \pm 13	119–199
DV	121 \pm 14	77–167

test yet of TCD prediction in children with SCD. The data enable testing of PSV and EDV in risk stratification, which is crucial to primary stroke prevention in these children. The comparison of stroke-free survival used in this analysis indicated that EDV, although associated with stroke risk, did not add information to the survival model after accounting for Tamm and PSV.

We interpret the conflicting results between forward selection and backward elimination modeling techniques as demonstrating that PSV and Tamm are approximately equivalent in terms of prediction. This is not surprising, as the two variables are highly correlated. The purpose of this study was not to replace Tamm but to provide alternative velocity cutpoints based on PSV.

Because of the variation in waveform shape in TCD among patients, unique PSV and EDV cutpoints that correspond precisely to the 170 and 200 cm/s Tamm boundaries used in STOP could not be derived. The large amount of data, however, allowed reasonable approximations to be made by examination of the distribution of velocities in relation to Tamm. Because EDV appears to offer no advantages over Tamm in stroke prediction, only PSV will be further considered. The choice of PSV that correlates with 170 and 200 cm/s Tamm involves a trade-off between sensitivity and specificity. The STOP criteria are based on maximum allowable velocities (<170 cm/s for low-risk or “normal” TCD and 200 cm/s as the threshold for high-risk or “abnormal” TCD). STOP did not use low velocity as a treatment criterion (although there is some evidence that very low velocities may indicate severe disease and be associated with risk [17]). Thus the upper limits of the “normal” and “conditional” categories are the meaningful boundaries to consider. Ideally, the PSV cutpoint for abnormal would include all or most of those classified as abnormal in STOP while including as few as

Table 4 PSV and DV from 206 abnormal TCD examinations

	Velocity (cm/sec)	
	Mean \pm SD	Range
PSV	298 \pm 31	245–420
Tamm	225 \pm 27	200–366
DV	163 \pm 28	120–308

Table 5 Distribution of PSV in 1358 TCD examinations normal by TAMM (<170 cm/s)

Quantile (%)	PSV (cm/s)
100 (max)	300
99	253
95	238
90	228
75 (Q3)	214
50 (median)	194
25 (Q1)	173
10	155
5	144
1	131
0 (min)	104

Table 7 Distribution of PSV in 206 TCD examinations abnormal by TAMM (≥ 200 cm/s in MCA or ICA)

Quantile (%)	Estimate
100 (max)	420
99	386
95	356
90	338
75 (Q3)	313
50 (median)	292
25 (Q1)	276
10	264
5	260
1	251
0 (min)	245

possible of those classified as conditional. The distributions of PSV relative to TAMM-defined categories are shown in Tables 5–7 and are provided so that the reader can evaluate directly the impact of various candidate cutpoints. For example, considering the cutpoint for abnormal, from Table 7 it can be seen that a PSV boundary of 264 cm/s includes 90% of STOP-defined high-risk children while excluding about 80% of conditional examination examinations (Table 6); a PSV boundary of 250 cm/s includes 99% of abnormal examinations but excludes approximately 50% of the conditionals. Changing the cutpoint to 275 cm/s excludes more than 90% of the conditional examinations, but 25% of STOP abnormal examinations would be defined as conditional.

Another factor that must be considered is that PSV cutpoints are most likely to be applied to data obtained from transcranial Doppler imaging (TCDI) systems rather than the dedicated Doppler used in STOP. There are data from side-by-side comparisons that can be used to adjust the TCDI velocities to make them comparable to STOP velocities. Comparisons of Acuson and ATL duplex TCDI machines, in direct comparison to data from the MCA in the same patients examined with the Nicolet (STOP) machine and using the same protocol, showed approximately 5–10% lower velocities recorded

Table 6 Distribution of PSV in 373 TCD examinations conditional by TAMM (≥ 170 –199 cm/s)

Quantile (%)	PSV (cm/s)
100 (max)	322
99	300
95	285
90	272
75 (Q3)	260
50 (median)	246
25 (Q1)	233
10	217
5	202
1	180
0 (min)	165

by the TCDI systems in two [11, 12] of the three published studies. This suggests that a PSV cutpoint used in practice from a TCDI system should be set somewhat lower than the PSV values reported here, which were derived from the TCD system to arrive at the same classification results reported in STOP. If this measurement bias is considered, 250 cm/s obtained from TCDI would correspond to a PSV shown in Tables 6 and 7 of approximately 270 cm/s. This would equate to a reasonable compromise of including about 83% of the abnormal examinations and excluding about 87% of the conditional examinations.

Accordingly, a TCDI-derived PSV of 250 cm/s is proposed as the threshold for transfusion consideration. It should be emphasized that two abnormal examinations exceeding this threshold separated by at least 1 week in clinically stable patients (no fever, no worsened anemia from baseline, no hypoxia) should be obtained to establish a sustained elevated velocity in keeping with the STOP study protocol. In STOP, two abnormal examinations were required in all patients prior to randomization, and 15% of children with one abnormal examination (usually at or slightly above the 200 cm/s boundary) had a second study, which did not reach 200 cm/s. More than 95% of the children whose first TCD TAMM was > 220 cm/s also had an abnormal result on the next examination. Accordingly, a single high-velocity study of 220 cm/s TAMM or two ≥ 200 cm/s TAMM was adopted as the standard for treatment selection after STOP. Using this logic, a single TCDI study that shows a PSV of 280 cm/s or more in either the MCA or distal ICA should be sufficient to establish the child as being at high risk. It must be emphasized that the criteria described here refer only to the MCA and ICA and assume that efforts are made to optimize the signal to obtain the highest velocity, a feature that is key to the STOP TCD protocol. No angle correction was used in the comparison studies.

Elevated velocities in the anterior, posterior or basilar arteries were not used to select patients for the STOP trial. There were insufficient data to suggest elevated

stroke risk when only these arteries had elevated TCD velocity. This does not mean that such patients are not at elevated risk, and they were classified as having conditional TCD and were under increased TCD surveillance. Seibert et al. [18] included these arteries in their classification system and reported an increased prevalence of cerebrovascular disease on MRI when TCD abnormalities were present in these vessels.

The selection of the upper boundary for normal using TCDI PSV measures is less critical because treatment is not recommended for those with moderate velocity (risk) elevation.

By TCDI, a PSV boundary between normal and conditional of 200 cm/s is recommended for the following reasons: using the 7.5% adjustment for TCDI values, a 200 cm/s TCDI-derived PSV would correlate to a TCD-derived PSV of 215 cm/s. At this cutpoint, from Tables 5 and 6 it can be seen that about 90% of the STOP conditionals would be classified by PSV as conditional, and about 75% of the STOP normals would fall below the cutpoint and be excluded. The authors consider this a reasonable cutpoint.

The data from the MCG cohort studies [3, 4] and STOP indicate that the risk of stroke increases with velocity in a linear fashion, making these cutpoints useful but somewhat arbitrary guidelines for management. Children in the high-conditional range are at considerably elevated risk compared to those in the normal range. The value of TCD is to provide an estimate of risk rather than to serve as an absolute determinant of clinical decisions. The PSV criteria recommended here are conservative in the sense that the numbers were chosen to maximize the opportunity to prevent stroke [19] while accepting a cost of greater use of resources (TCD screening) to accomplish this goal, and a greater use of transfusion if these criteria are used.

In conclusion:

1. PSV and diastolic velocities are highly correlated with TAMM and all three velocities are highly predictive of future stroke in children with SCD.
2. PSV is at least as good as, and may be better than, TAMM for stroke prediction while diastolic systolic velocity is not as good a predictor as TAMM or PSV.
3. Taking into consideration that most TCDI systems measure MCA velocity about 7.5% lower than the TCD used in STOP, a TCDI PSV of 200 cm/s is recommended to define a conditional TCD result, which should lead to increased TCD and clinical surveillance.
4. A PSV derived from TCDI (with a zero angle of insonation) in either the MCA or inner cerebral artery of 250 cm/s is comparable to a TCD-measured TAMM of 200 cm/s, the threshold at which to consider prophylactic treatment, if confirmed on a second test. A single TCDI-derived PSV of 280 cm/s in the MCA or ICA is sufficient to establish high risk and should lead to consideration for chronic transfusion based on the STOP study results.
5. The data presented in this study do not indicate whether substantial benefit would result from converting all treatment surveillance recommendations to PSV from TAMM. The authors recommend using TAMM cutpoints if screening with TCD and PSV cutpoints if screening with TCDI.

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