

# Impact of MRA Echo Time on Stroke Prevention Therapy in Pediatric Patients with Sickle Cell Disease

Parmpreet Dhillon<sup>1</sup>, Kerry Morrone<sup>1</sup>, Kevin Hsu<sup>1</sup>, William Gomes<sup>2</sup>, Ellen Silver<sup>3</sup>, Daniel Lax<sup>1</sup>, Qi Peng<sup>1</sup>, Seon Kyu Lee<sup>1</sup>, Deepa Manwani<sup>1</sup>, and William Mitchell<sup>3</sup>

<sup>1</sup>Montefiore Medical Center

<sup>2</sup>Westchester Medical Center

<sup>3</sup>Yeshiva University Albert Einstein College of Medicine

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## Abstract

**Background:** Flow artifact, intrinsic to Magnetic Resonance Angiography (MRA), is dependent on technical parameters and can lead to overinterpretation of stenosis. Degree of cerebrovascular stenosis in pediatric patients with sickle cell anemia (SCA) informs need for chronic transfusion therapy, which may have significant risks. The primary objective of this study was to document any change in stroke prevention therapy that could be attributed to the implementation of a standardized MRA scanning protocol. **Procedure:** A standardized MRA scanning protocol with an echo time of <5 msec was implemented at Montefiore Medical Center in May 2016. Retrospective chart review identified 29 patients [?] 21 years with SCA cerebral vasculopathy and an MRA head pre- and post-May 2016. Level of arterial stenosis on MRA, echo time, and treatment plans were documented both pre- and post-implementation. McNemar analysis determined the significance of change in treatment plans before and after implementation of the standardized scanning protocol. **Results:** Previously seen stenosis was re-classified to a lower degree in 12/29 patients (41%). Notably, 6 patients had a reclassification of vasculopathy leading to discontinuation of chronic transfusion therapy whereas 0 patients required escalation of therapy to chronic transfusions. McNemar analysis showed this difference to be statistically significant ( $p = 0.042$ ). **Conclusion:** Minimizing flow artifact with echo time <5msec improves accurate interpretation of true cerebrovascular disease and ensures appropriate treatment plans are in place for stroke prevention. This is especially important when trying to implement “TCD With Transfusions Changing to Hydroxyurea (TWiTCH)” clinical trial results in the real-world setting.

## Impact of MRA Echo Time on Stroke Prevention Therapy in Pediatric Patients with Sickle Cell Disease

*Authors:* Parmpreet Dhillon, MD<sup>1</sup>, Kerry Morrone, MD<sup>2</sup>, Kevin Hsu, MD<sup>3</sup>, William Gomes, MD, PhD<sup>4</sup>, Ellen Silver, Ph.D<sup>5</sup>, Daniel Lax MD<sup>1</sup>, Qi Peng, PhD<sup>6</sup>, Seon Kyu Lee MD, PhD<sup>3</sup>, Deepa Manwani, MD<sup>2</sup>, William Mitchell, MD<sup>2</sup>

<sup>1</sup>Division of Child Neurology, Department of Neurology, Montefiore Medical Center / Albert Einstein College of Medicine

<sup>2</sup> Division of Hematology/Oncology, Department of Pediatrics, Children’s Hospital at Montefiore, Albert Einstein College of Medicine

<sup>3</sup>Division of Neuroradiology, Department of Radiology, Montefiore Medical Center / Albert Einstein College of Medicine

<sup>4</sup>Division of Neuroradiology, Department of Radiology, Westchester Medical Center and New York Medical College

<sup>5</sup>Division of Academic General Pediatrics, Children’s Hospital at Montefiore, Albert Einstein College of Medicine

<sup>6</sup>Department of Radiology, Montefiore Medical Center / Albert Einstein College of Medicine

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Corresponding Author: Parmpreet Dhillon, MD

1410 Pelham Pwy South - Kennedy 316 Bronx, N.Y. 10461

Phone: 718-430-2447

Fax: 216-208-1053

pampreetdhillonmd@gmail.com

Running Title: Impact of MRA TE on SCD Stroke Prevention Therapy

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MeSH Index Terms: Magnetic Resonance Angiography, artifacts, stroke, sickle cell, cerebrovascular disease

Abbreviation	Full term
MMC	Montefiore Medical Center
MRI	Magnetic Resonance Imaging
MRA	Magnetic Resonance Angiography
SCD	Sickle Cell Disease
SCA	Sickle Cell Anemia

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### Procedure:

A standardized MRA scanning protocol with an echo time of <5 msec was implemented at Montefiore Medical Center in May 2016. Retrospective chart review identified 29 patients [?] 21 years with SCA cerebral vasculopathy and an MRA head pre- and post-May 2016. Level of arterial stenosis on MRA, echo time, and treatment plans were documented both pre- and post-implementation. McNemar analysis determined the significance of change in treatment plans before and after implementation of the standardized scanning protocol.

### Results:

Previously seen stenosis was re-classified to a lower degree in 12/29 patients (41%). Notably, 6 patients had a reclassification of vasculopathy leading to discontinuation of chronic transfusion therapy whereas 0 patients required escalation of therapy to chronic transfusions. McNemar analysis showed this difference to be statistically significant ( $p = 0.042$ ).

### Conclusion:

Minimizing flow artifact with echo time  $<5$  msec improves accurate interpretation of true cerebrovascular disease and ensures appropriate treatment plans are in place for stroke prevention. This is especially important when trying to implement “TCD With Transfusions Changing to Hydroxyurea (TwiTCH)” clinical trial results in the real-world setting.

## Introduction

In pediatric patients with sickle cell anemia (SCA), stroke is a major cause of morbidity and mortality with an estimated 1.9-11% risk of stroke by the age of 20 (1-7). Specific screening and treatment guidelines aimed at both primary and secondary prevention have successfully reduced the incidence of overt strokes in this high-risk population (4). The Stroke Prevention Trial in Sickle Cell Anemia (STOP) trial showed significant primary stroke prevention by reducing the risk of first stroke by 90% with chronic transfusions in those patients at increased risk as determined by Transcranial Doppler (TCD) (4). This study led to a national recommendation to conduct annual TCD screening for all children with SCA between the ages of 2-16 years (8).

Patients with SCA who have conditional or abnormal TCDs or neurologic symptoms may undergo regular neuroimaging with Magnetic Resonance Imaging (MRI) and Magnetic Resonance Angiogram (MRA) to confirm cerebral vasculopathy and stratify stroke risk. Risk stratification using MRA is recommended by the American Society of Hematology in selection of a stroke prevention treatment plan (9). Current recommendations based on the multicenter, randomized controlled trial TwiTCH (TCD with Transfusions Changing to Hydroxyurea) suggest that a child aged 2-16 with abnormal TCD results who has been receiving transfusion therapy for at least 1 year with low-risk MRA imaging can be transitioned off transfusions and onto hydroxyurea treatment (9, 10). Determination of low-risk or high-risk requires MRA grading of vasculopathy, highlighting the importance of accurate MRA assessment.

Standard non-contrast MRA is accomplished with a 3-dimensional time of flight technique and allows assessment of the patency and caliber of intracerebral arterial vessels (11). Technical artifacts can influence the appearance of arterial structures on MRA (12), especially in regions of arterial tortuosity or bifurcation, sites commonly affected in patients with SCA. These technical artifacts can lead to the erroneous interpretation of arterial stenosis, and thereby lead to inappropriate risk stratification and treatment selection for primary stroke prevention, such as initiation or continuation of chronic transfusion therapy or transition to hydroxyurea. While chronic transfusion therapy can significantly lower stroke risk (13), it has notable risks including iron overload, alloimmunization, and infection (14-16).

Investigators in the Stroke with Transfusions Changing to Hydroxyurea (SWiTCH) trial developed standardized scanning protocols for their entry and exit brain MRI, MRA, and TCD studies. The SWiTCH MRA scanning protocol specified an echo time of  $<5$  msec (12). Echo time or TE, describes the time between application of radiofrequency excitation pulse and peak of the signal induced in the coil, measured in milliseconds (msec). While SWiTCH primary objective was to compare standard transfusion therapy to hydroxyurea in preventing recurrent stroke and quantitative liver iron content (12), the standardized imaging scanning protocols developed provide an opportunity for further study of flow artifact and its clinical importance. These MRA scanning protocols were also utilized in the TwiTCH trial to grade vasculopathy as low and high risk and guide treatment decisions. The generalizability and real-world application of the results of the TwiTCH trial could potentially depend on close adherence to study MRA protocols. Few reports have mentioned minimizing TE to  $<5$  msec to limit flow-related artifact (5, 6, 17), however, no prior studies have reported the clinical implications of these protocols.

The primary objective of our study was to document any change in stroke prevention therapy, particularly discontinuation of chronic transfusions, that could be attributed to the implementation of the standardized MRA scanning protocol based on the SWiTCH protocol. We hypothesized that the implementation of a standardized MRA protocol would lead to re-classification of the level of cerebral stenosis and impact treatment plan for a subset of patients.

## Methods

At Montefiore Medical Center (MMC), a standardized MRA scanning protocol with TE <5 msec based on the SWiTCHe protocol was implemented in May 2016. This study was approved by the Albert Einstein College of Medicine and MMC Institutional Review Board as a retrospective chart review that included the following criteria i) patients [?]21 years old at the time of implementation of the scanning protocol in May 2016 ii) sickle cell disease (genotypes SS, S $\beta$ 0thalassemia, S $\beta$ +thalassemia, SC), iii) established hematology care at CHAM for at least one year (defined as having at least one outpatient clinic visit), and iv) MRA performed at MMC prior to May 1<sup>st</sup> 2016 AND after May 1<sup>st</sup> 2016.

Clinical Looking Glass (CLG), a patented software tool designed by MMC for practitioners to use medical and administrative data as a means for continued quality improvement, was used to identify study population. Inclusion criteria applied to CLG were ICD diagnoses for sickle cell disease, age [?]21, date range of 2014-2018, and procedure codes for MRI. Studies performed on MRI machines from any vendors and any MMC sites were included. Exclusion criteria included incomplete records and patients with only one MRA. Twenty-nine patients were identified with any degree of cerebral vasculopathy on the pre-May 2016 images and included in this study. Patient assembly including ICD codes is illustrated in Figure 1.

A dedicated neuroradiologist with expertise in interpreting vasculopathy in sickle cell patients reviewed all images as part of institutional hematology-neuroradiology rounds that are performed as a routine component of clinical care. After data collection and prior to analysis, a separate blinded neuroradiologist reviewed key images for patients in question. Level of arterial stenosis on MRA, TE, and treatment plans were documented both pre- and post-May 2016 for each patient. Other technical factors such as magnet field strength, repetition time (TR) and slice thickness were also noted.

A McNemar analysis was performed to determine whether there was a significant change in treatment plan after implementation of the standardized MRA scanning protocol.

## Results

Baseline demographics and treatment plans for the 29 patients with sickle cell CNS vasculopathy prior to implementation of the MRA scanning protocol in May 2016 are listed in Table 1. Indications for chronic transfusion therapy included primary stroke prevention for 7 patients, secondary stroke prevention for 17 patients, and chronic pain for 2 patients.

MRAs were performed for routine screening, symptoms including headache, or focal neurologic findings. Pre-May 2016, 16/29 patient studies used TE <5msec whereas post May 2016, 26/29 patient studies used TE <5msec.

For 12 of the 29 patients (41%), some or all stenosis that was previously seen on pre- May 2016 MRA imaging was not identified on MRA imaging done post- May 2016. Figures 2 and 3 show examples of MRAs in two patients in whom vasculopathy was no longer visualized. In six patients, there was a decrease in the classification of CNS vasculopathy, however, their treatment was not impacted. These patients were not on disease modifying therapy, already had significant stenosis requiring transfusions, or had undergone curative bone marrow transplant.

In six patients (21%) there was complete resolution of previously seen CNS vasculopathy that lead to a change in treatment plan; all six patients were on chronic transfusion therapy for primary stroke prevention and after review of newer imaging showing no vasculopathy, this therapy was discontinued. Two patients had an increase in the degree of classification of stenosis, suggestive of the commonly seen progression of sickle cell CNS vasculopathy, without change in their treatment plan.

As seen in Figure 4, 24 patients (83%) were on chronic transfusion therapy prior to May 2016, while this number decreased to 18 (62%) after May 2016. For the McNemar analysis (Table 2), clinical treatment plans were categorized as “Transfusions” or “Not transfusions” both pre- and post- implementation of the scanning protocol. 18 patients remained in the same category of requiring transfusion therapy pre- and post- implementation. While six patients on chronic transfusion therapy were able to discontinue transfusion therapy, 0 patients required escalation in treatment plan (starting chronic transfusion therapy). Five patients

with CNS vasculopathy remained off chronic transfusion therapy. The proportion of patients with change in treatment plan after the implementation of scanning protocol with TE < 5msec was found to be statistically significant ( $p = 0.0412$ ).

## Discussion

Accurate diagnosis of large vessel narrowing has clinical implications for stroke risk stratification and the initiation of and escalation of clinical interventions such as transfusions and surgical procedures (e.g. encephaloduroarteriosynangiosis) in pediatric patients with SCA. While there are many imaging techniques to examine the intracranial vasculature, MRA imaging without gadolinium is preferred as first line as it is noninvasive, avoids ionizing radiation and iodinated or gadolinium contrast, compared to Computed Tomography Angiography (CTA), catheter angiography, and contrast-enhanced MRA(18). Non-contrast MRA provides visual assessment of flow-related enhancement within the intracranial arteries as compared to velocity assessment with TCD, however it is uniquely subject to flow-related MRI artifact, which can lead to misidentification of stenosis when it is not truly present, or exaggeration of existing stenosis.

One disadvantage of noncontrast MRA is the potential loss of flow-related signal in regions of arterial tortuosity and/or branching, which are commonly present in patients with SCA, and the possibility for this artifact to simulate arterial stenosis. The possibility of artifactual stenosis is especially problematic in SCA, as the regions typically affected by artifact on noncontrast MRA overlap with the regions typically affected by sickle-cell related vasculopathy. Use of short-TE MRA techniques (ideally less than 5msec), can limit the artifactual loss of flow-related signal and thereby more accurately assess the true patency of intracerebral arterial vessels.

Of the 29 patients initially identified with sickle cell CNS vasculopathy, our study identified 12 patients (41%) in whom the level of cerebral stenosis was re-classified to a lower degree after implementation of the standardized MRA protocol. Clinically, an improvement in the level of arterial stenosis is not expected in patients with SCA, even for those on disease modifying therapy such as chronic transfusion therapy. This suggests that previously identified areas of stenosis were a result of artifact rather than true vasculopathy.

In six patients (21%) this reclassification led to a de-escalation of the stroke prevention plan and discontinuation of chronic transfusion therapy. In these six patients, the initially identified stenosis was noted to be most often in A1 branch of the anterior cerebral artery or supraclinoid segments of the internal carotid artery. Additionally, one patient was newly identified to have stenosis and one patient was determined to have an increased classification of stenosis, suggesting a progression of stenosis due to SCA.

As a retrospective chart review, this study has limitations in assessing whether the TE of the scanning protocol is responsible for leading to the decreased appearance of artifact and thus clinical change in treatment plan. After May 2016, MRA in three patients had TE >5msec, suggesting that the standardized scanning protocol was not uniformly implemented at our institution in May of 2016. For the six patients in which the degree of CNS stenosis was re-classified and treatment was de-escalated, two patients had TE > 5msec on their post May 2016 imaging. While TE was the major parameter standardized in this protocol, MRA time of flight angiography phase dispersions may also be dependent on other technical parameters. For example, a greater slice thickness or TR will make the contrast between stationary tissue and blood less obvious. To evaluate this, TR, matrix size, and slice thickness were reviewed for several patients and were not noted to be significantly different.

Our analysis included 29 patients; however, our initial chart sample identified 136 patients with only one MRA; reanalysis of all MRA exams done prior to May 2016 or with a high TE may identify other patients in which the stenosis can be re-classified.

Aside from the presence of MRI artifacts, interpretation of MRA imaging may be partially dependent on the interpreting neuroradiologist. To minimize this variability, a blinded expert neuroradiologist reviewed the pre-May 2016 images for the six patients that had a change in treatment plan. This reader agreed with previous MRA reports regarding the appearance of stenosis in five of the six patients, however for one patient

this reader did not identify any stenosis on the pre-May 2016 imaging. This raises the question regarding variability of expert neuroradiologist interpretation of stenosis versus artifact in scans with higher TE and implications on clinical management.

To elucidate these results further, next steps could include a focused comparative analysis of TCD and MRA findings on a larger sample size, which may require a multicenter project to identify patients with CNS arterial stenosis identified using a higher TE and prospectively re-image them with a lower TE. Further analysis could also include other factors that might decrease the degree of artifact (slice thickness, matrix, contrast mechanisms, etc.), comparison to other vessel imaging techniques, long term follow up of patients identified in this study, and addressing the impact of MRI parameters in patients with other vascular conditions.

### Conclusion

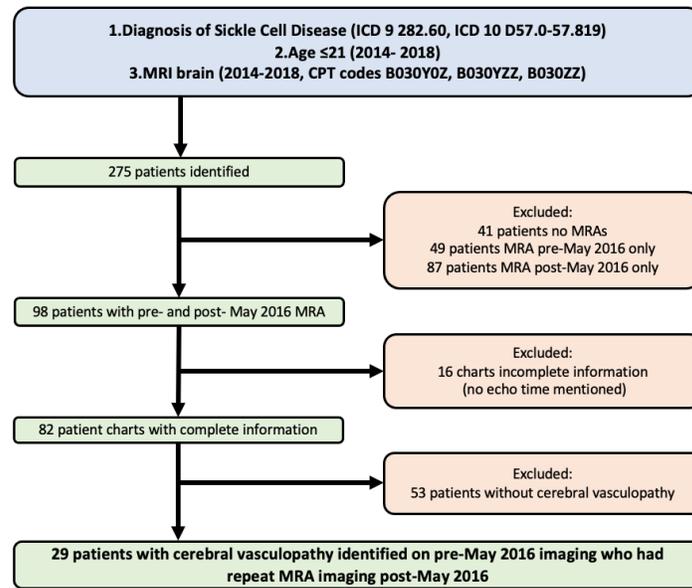
Implementing a standardized, SCA-specific MRA scanning protocol, using short-TE techniques, allowed for re-classification of previously seen stenosis in 12/29 patients (41%). This reclassification resulted in discontinuation of chronic transfusion therapy, which has potentially significant side effects, in six out of 24 patients. Implementation of the TWiTCH trial results is dependent on accurate classification of the grade of vasculopathy on MRA and if low grade, allows the patients to transition to hydroxyurea. Optimizing MRA echo time to <5msec can minimize flow artifact, improve accurate interpretation of true cerebrovascular disease, and impact treatment plans put in place for stroke prevention for pediatric patients with sickle cell anemia.

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**Figure 1. Flowchart of patient sample identification**



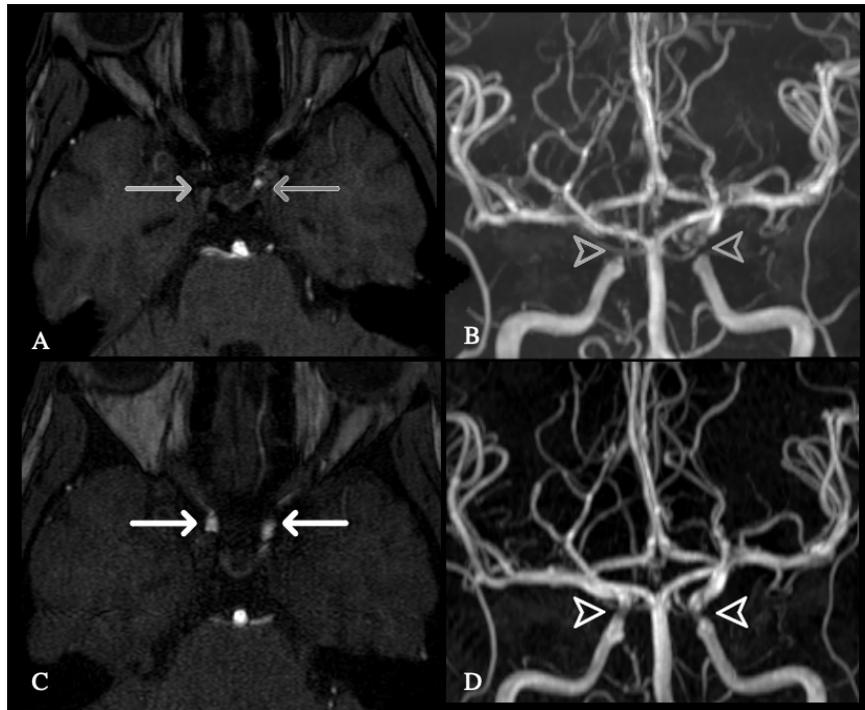
**Table 1. Baseline (pre-May 2016) clinical characteristics of 29 patients with sickle cell CNS vasculopathy**

Variable	Value
Age <b>median (range), y</b>	12 (5-21)
<b>Sex</b>	<b>n (%)</b>
Male	12 (41)
Female	17 (59)
<b>Genotype</b>	<b>n (%)</b>
HgbSS	29 (100)
<b>Clinical treatment plan</b>	<b>n (%)</b>
Hydroxyurea	2 (7)
Chronic transfusion therapy	19 (66)
Previous Bone Marrow Transplant	1 (3)
Previous Bone Marrow Transplant + chronic transfusions	5 (17)
EDAS* + chronic transfusions	2 (7)
<b>Degree of objective neurologic disease</b>	<b>n (%)</b>
None	8 (27)
TIA (clinically)	2 (7)
Silent infarct	18 (62)
Symptomatic stroke	11 (38)

\* Encephaloduroarteriosynangiosis

**Figure 2. Example patient images**

Axial 3D time of flight (TOF) MRA head and corresponding maximum intensity projection (MIP) images before (A, B) and after (C, D) the protocol change in the same patient.



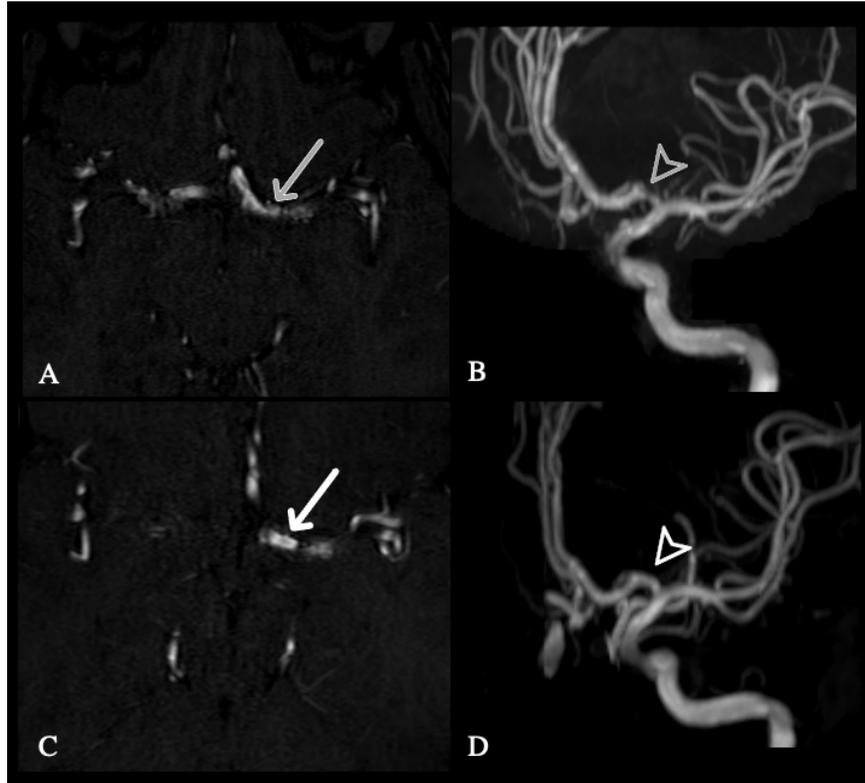
Before - Images A and B taken with a higher echo time show focal diminished flow related signal in the right

greater than left internal carotid artery supraclinoid segment (outlined grey arrow and arrowhead).

After - Images C and D taken with a lower echo time show vessel patency after protocol change (white arrow and white arrowhead).

### Figure 3. Example patient images

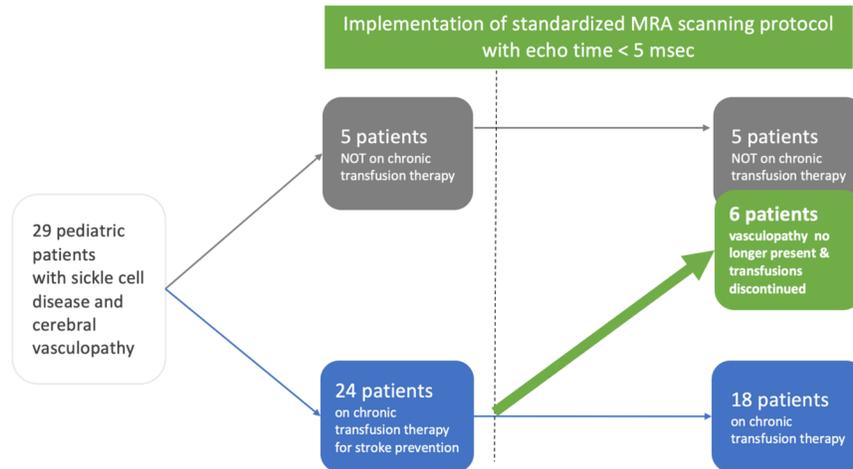
Axial 3D time of flight (TOF) MRA head and corresponding maximum intensity projection (MIP) images before (A, B) and after (C, D) the protocol change in the same patient.



Before - Images A and B taken with a higher echo time show focal diminished flow related signal in the A1 segment of the left anterior cerebral artery (outlined grey arrow and arrowhead).

After - Images C and D taken with a lower echo time show vessel patency after protocol change (white arrow and white arrowhead).

### Figure 4. Treatment plans for 29 patients with sickle cell CNS vasculopathy pre and post implementation of a standardized MRA scanning protocol



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Data available on request due to privacy/ethical restrictions

#### *Figure Legend*

*Figure 1.* Flowchart of patient sample identification

*Table 1.* Baseline (pre-May 2016) clinical characteristics of 29 patients with sickle cell CNS vasculopathy

*Figure 2.* Example patient images

Axial 3D time of flight (TOF) MRA head and corresponding maximum intensity projection (MIP) images before (A, B) and after (C, D) the protocol change. Before - Images A and B taken with a higher echo time show focal diminished flow related signal in the right greater than left internal carotid artery supraclinoid segment (outlined grey arrow and arrowhead). After - Images C and D taken with a lower echo time show vessel patency after protocol change (white arrow and white arrowhead).

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*Figure 4.* Treatment plans for 29 patients with sickle cell CNS vasculopathy pre and post implementation of a standardized MRA scanning protocol

#### *Data Availability*

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

#### **Hosted file**

Tables Impact of MRA Echo Time on Stroke Prevention Therapy in Pediatric Patients with Sickle Cell Disease available at <https://authorea.com/users/473807/articles/563870-impact-of-mra-echo-time-on-stroke-prevention-therapy-in-pediatric-patients-with-sickle-cell-disease>

