



RESEARCH ARTICLE

Vascular Geometry Drives Stroke Risk in Sickle Cell Disease

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Received: 28 July 2025 | **Revised:** 10 December 2025 | **Accepted:** 18 December 2025

Keywords: cerebral hemodynamics | cerebral vasculopathy | computational modeling | sickle cell disease | stroke risk | vascular geometry

ABSTRACT

Sickle cell disease (SCD) is the leading cause of stroke in children and young adults, primarily due to cerebral vasculopathy (CV) occurring within the first decade of life. The main risk factor for CV is elevated blood velocity in intracranial arteries, contributing to stenosis formation in very young children. This study addresses three key questions: (i) the relationship between hemoglobin levels and intracranial blood velocities in SCD patients, (ii) additional factors contributing to elevated velocity beyond anemia, and (iii) the presence of flow anomalies. To investigate these aspects, biological and transcranial Doppler data from pediatric and adult SCD patients were analyzed. An image-based *in silico* modeling approach was also developed to simulate blood flow in the internal carotid, anterior cerebral, and middle cerebral arteries of SCD patients, of different age classes, and prior to any possible stenosis. Analysis revealed that while anemia is a recognized CV risk factor, it does not fully explain elevated velocities, as no significant correlation was found in children under five. In *in silico* simulations, young patients reached pathological arterial intracranial velocities at physiological flow rates, whereas adults remained below risk thresholds even at high flow rates. Pathological velocities were primarily observed in distal internal carotid arteries, where stenoses often develop. High flow rates, small arterial diameters, and pronounced curvatures led to extreme velocities and complex flow, likely causing endothelial damage and promoting CV progression. These findings enhance understanding of hemodynamic mechanisms underlying SCD-related stroke risk, paving the way for improved predictive models and early interventions.

Trial Registration: ClinicalTrials.gov identifier: NCT05199766.

1 | Introduction

Sickle cell disease (SCD) is the most prevalent inherited blood disorder worldwide. It is caused by a single mutation in the

β -globin gene, leading to the production of abnormal hemoglobin (HbS). Upon deoxygenation, HbS polymerizes, resulting in the characteristic sickle shape of red blood cells. These morphological changes increase the rigidity and fragility of red blood

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cells, leading to vaso-occlusive events and hemolytic anemia, which can cause complications in multiple organs.

Among SCD complications, cerebral vasculopathy (CV) is the leading cause of stroke in children and young adults [1–3]. Interestingly, SCD-related CV appears quite exclusively in young children, in contrast to other progressive organ dysfunctions, which are associated with aging (i.e., pulmonary hypertension or cardiac dysfunction). The primary risk factor for the development of CV in SCD is increased blood velocity in the intracranial vessels. These high velocities, particularly observed in the internal carotid arteries (ICA), anterior cerebral arteries (ACA), and middle cerebral arteries (MCA), are associated with a 40% risk of stroke within 3 years when the time-averaged maximum velocity (TAMV) exceeds 200 cm per second on transcranial Doppler (TCD) ultrasound [4, 5]. These accelerations occur mainly in children aged 2 to 12 years [6], most often before 5 years. They usually precede the appearance of arterial lesions detected by magnetic resonance angiography (MRA), suggesting that high blood velocity is rather the cause and not the consequence of stenosis formation [4, 7, 8].

Anemia is a well-established risk factor for cerebral vasculopathy in SCD. Variations in hemoglobin (Hb) levels influence blood viscosity [9] and cerebrovascular hemodynamics [10]. However, while anemia leads to a compensatory increase in cardiac output and cerebral blood flow, it is unlikely to be the sole determinant of the accelerated intracranial blood velocities observed in these patients. The marked interindividual variability in blood flow velocities, independent of other clinical factors, along with the asymmetry observed within the same patient, suggests the involvement of additional mechanisms. We hypothesized that the unique cerebrovascular architecture of young children contributes to this phenomenon. The intracranial arterial anatomy and flow territories of children differ from those of adults [11], and children with SCD exhibit even higher intracranial velocities and more pronounced hemodynamic alterations than their peers without SCD [12], suggesting a specific hemorheological milieu that may further accelerate intracranial blood velocities.

This study aims to elucidate key aspects of this complex mechanism by addressing three pivotal and interconnected questions: (i) what is the relationship between elevated intracranial blood velocities and hemoglobin levels in individuals with SCD, and does this relationship vary with age? (ii) what other factors, beyond anemia, may contribute to this elevation in velocities? and (iii) are these increased velocities associated with flow anomalies?

To investigate these questions, we first analyzed biological and TCD data from a cohort of pediatric and adult SCD patients, and then developed an image-based in silico modeling approach to simulate cerebral blood flow within patient-specific geometries of the intracranial arteries.

2 | Methods

2.1 | Study Cohort

This study was conducted using a cohort of SCD patients, comprising both pediatric and adult populations. The pediatric cohort consisted of children with SCD followed at the Centre Hospitalier

Intercommunal de Crétel (Crétel, France), while the adult cohort was derived from the HEMOPROVE study (NCT05199766), which included SCD patients followed at the Henri-Mondor University Hospital (Crétel, France). All patients included in these cohorts had, at a minimum and within the same timeframe, a comprehensive biological assessment and a TCD evaluation measuring internal carotid arteries (ICA), anterior cerebral arteries (ACA), and middle cerebral arteries (MCA) velocities.

Firstly, the entire cohort was used to investigate the relationship between hemoglobin levels and intracranial blood flow velocities.

In a second phase, a subset of patients from different age groups (under 5 years, 5 to 18 years, and over 18 years) with high-quality brain MRA scans was selected for detailed vascular segmentation and in silico modeling.

2.2 | Imaging Acquisition and Segmentation

Patient-specific 3D geometries were reconstructed from time-of-flight MRA sequences using 1.5T or 3T scanners. Isolated arterial trees containing the ICA from entry into the petrous bone to the termination and initial portion of the MCA and ACA were segmented from MRA with the software Materialise Mimics (Figures S1 and S2) [13].

2.3 | 3D Mathematical Model and Blood Flow Simulations

Blood flow was numerically simulated by solving the 3D Navier-Stokes equations of fluid mechanics (Figure S3) [14, 15]. Based on our cohort data from SCD patients, blood viscosity was set to a baseline value of 0.04 Poise, and inlet mean flow rates at the ICA were varied from 2.5 to 15 mL/s. Pulsatile flow was assigned as an inlet boundary condition. Blood velocities were computed in five regions of interest (ROIs) in each artery: the proximal ICA, ICA cavernous segment (called siphon), distal ICA, ACA, and MCA (Figure S2D).

2.4 | Assessment of Flow Complexity

To analyze flow complexity, referred to as turbulence in some medical studies [16], we evaluated the Reynolds number and the Dean number. The Reynolds number is a key parameter for determining whether a flow is laminar or turbulent. The Dean number specifically characterizes flow behavior in curved conduits, such as bent arteries, where centrifugal forces influence the flow dynamics.

2.5 | Machine Learning

The influence of geometric properties of the proximal ICA, siphon, and distal ICA on blood flow velocity values was investigated with a random forest regression model. The in silico data set was divided into a training set (75%) and a test (25%) set for model assessment.

Further details are provided in [Supporting Information Methods](#).

3 | Results

3.1 | Association Between Hemoglobin Levels and Intracranial Velocities

The cohort consisted of 128 patients: 24 children under 5 years old (<5 years group), 72 children over 5 years old (≥ 5 years group), and 32 adults over 18 years old (Adult group).

In the overall cohort, lower hemoglobin levels and younger age were independently associated with higher intracranial flow velocities across all investigated intracranial arteries (Table S1). However, when analyses were stratified by age group in children, differences emerged.

In children over 5 years old, hemoglobin levels were strongly correlated with intracranial velocities across all six examined regions, with correlation coefficients ranging from -0.32 to -0.56 . The strongest correlations were observed in the internal carotid arteries (right ICA: -0.42 ; left ICA: -0.56) (Figure 1B).

In children under 5 years old, a correlation was also noted between hemoglobin levels and flow velocities in the internal carotid arteries, but to a lesser extent (right ICA: -0.40 ; left ICA: -0.39). Importantly, however, no significant association was observed between hemoglobin levels and velocities in the ACA or MCA in this younger population (Figure 1A). This key finding supports the conclusion that anemia alone cannot fully explain the high intracranial blood velocities that lead to cerebral vasculopathy in very young children with sickle cell disease, suggesting that their unique vascular geometry may play a critical role. This hypothesis is consistent with developmental imaging data indicating age-related variations in the caliber of intracranial arteries and the distribution of blood flow between children and adults [11], and with 4D-flow MRI studies reporting higher intracranial flow and altered hemodynamics in children with SCD compared to their non-SCD peers [12].

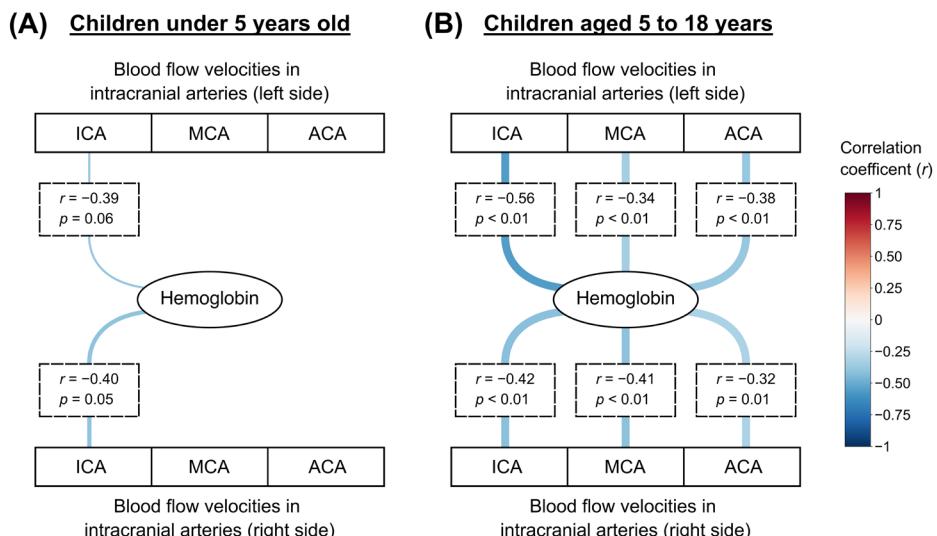


FIGURE 1 | Correlation of hemoglobin levels with intracranial artery velocities measured by transcranial Doppler in the study cohort. (A) Subgroup analysis for children under 5 years. (B) Subgroup analysis for children aged 5 to 18 years. Connective lines between hemoglobin levels and intracranial artery velocities are colored based on the strength and direction of the correlation (red: positive correlation, blue: negative correlation). Line thickness scales with statistical significance based on p -values. Negligible connections are omitted ($p > 0.1$). ICA: internal carotid arteries; MCA: middle cerebral arteries; ACA: anterior cerebral arteries. [Color figure can be viewed at wileyonlinelibrary.com]

3.2 | A New Age-Stratified Cohort for In-Depth Analysis of Intracranial Artery Morphology and Hemodynamics in SCD

Building on these findings, a new cohort consisting of 15 patients with high-quality brain MRA was included in the segmentation protocol: 5 children under 5 years old (<5 years group), 5 children over 5 years old (≥ 5 years group), and 5 adults over 18 years old (Adult group). The median age was 4.7 years [4.2–4.7] in the <5 years group, 7.7 years [5.9–11.3] in the ≥ 5 years group, and 26.5 years [22.1–37.9] in the Adult group ($p = 0.002$). All patients had an SS genotype. The sex ratio (female/male) was 1.5 and similar in each group. The morphological characteristics were significantly different between the three groups in terms of height ($p = 0.004$), weight ($p = 0.002$), and BMI ($p = 0.003$). There was no significant difference between groups according to hydroxyurea treatment ($p = 0.7$) nor blood exchange transfusion programs ($p = 0.3$). Biological parameters under treatment were comparable between groups for hemoglobin levels ($p = 0.8$). Hemoglobin percentages were also statistically comparable for HbS ($p = 0.6$), HbA ($p = 0.2$), and HbF ($p = 0.058$) (Table S2).

3.3 | Geometric Determinants of Pathological Blood Velocities in Young Children With SCD

Key geometrical features of the internal carotid artery were analyzed for the 15 selected patients (Figure 2). Arterial diameter increased slightly with age, revealing a statistically significant difference between the <5 years group and the Adult group ($p < 0.01$). The curvature of the ICA siphon region was lower in the Adult group compared to the pediatric groups ($p < 0.05$). However, no significant differences were observed in tortuosity or torsion of the siphon region (Figure S4). Additionally, the shape factor -reflecting ellipticity in the ICA siphon region- was higher in adults than in children.

Taken together, these findings suggest that the combination of smaller vessel diameter and increased curvature in very young patients creates a vascular geometry that favors accelerated blood velocity and may contribute to early cerebrovascular risk.

3.4 | Age-Dependent Susceptibility to Pathological Blood Velocities Under Varying Cerebral Blood Flow Conditions in SCD

Building upon insights from vascular geometry, blood flow velocity in the ICA and its terminal branches (MCA and ACA) was simulated across the cardiac cycle for all patients (Figure 3).

At a mean ICA inlet flow rate of 10 mL/s, only patients in the <5 years group reached the critical threshold of 200 cm/s for the TAMV in the ICA siphon and distal sections (Figure 3A). In these regions, TAMV values were significantly higher in the <5 years group compared to the ≥5 years group ($p < 0.05$) and the Adult group ($p < 0.01$). Although it did not exceed the critical TAMV in the proximal ICA, velocities remained significantly higher in the <5 years group than in the Adult group ($p < 0.01$).

Peak systolic velocity analysis at 10 mL/s confirmed higher values in the <5 years group, especially in the distal ICA and downstream segments, and occasionally in the proximal ICA (Figure 3B). In the ≥5 years group, only 30% of geometries exceeded 200 cm/s, limited to distal ICA and MCA regions. No adult exceeded the threshold in any region.

Simulations with varying inlet flow rates (ranging from 2.5 to 15 mL/s) indicated that TAMV increased with inlet flow rate across all segments and age groups (Figure 3C, Figure S5). The

ICA siphon and distal regions were the first to cross the 200 cm/s threshold, notably at just 7.5 mL/s in the <5 years group. In contrast, adults only approached this level at the highest simulated flow rate (15 mL/s).

In summary, very young patients reached pathological velocities at physiologically normal flow rates, older children only occasionally at higher rates, and adults never did—highlighting the combined role of vascular geometry, anatomy, and anemia in early cerebrovascular risk in SCD.

3.5 | Flow Complexity as a Hemodynamic Marker of Early Vascular Alterations in SCD

Flow complexity in intracranial arteries was assessed across all regions of interest for all 15 patients, revealing strong correlations with TAMV (Pearson correlation coefficient: 0.71) (Figure 4B). The average Dean number—reflecting curvature-driven flow instability—decreased with age, indicating a reduction in flow disturbance across groups (Figure 4C).

An individual case analysis in a pediatric patient (<5 years group, patient #4) revealed distinct flow patterns and asymmetric blood flow acceleration between the left and right ICA (Figure 4D, Video S1). At identical inlet flow rates, velocity was notably higher in the right ICA siphon. Geometric analysis revealed similar diameters and torsion between sides, but greater curvature on the right. This curvature coincided with more complex and distorted flow downstream, despite comparable inflow profiles entering both siphon regions.

In summary, this study underscores a strong link between flow complexity, vessel curvature, and elevated velocities, supporting the hypothesis that hemodynamic disturbances may precede and predict stenosis formation in young SCD patients.

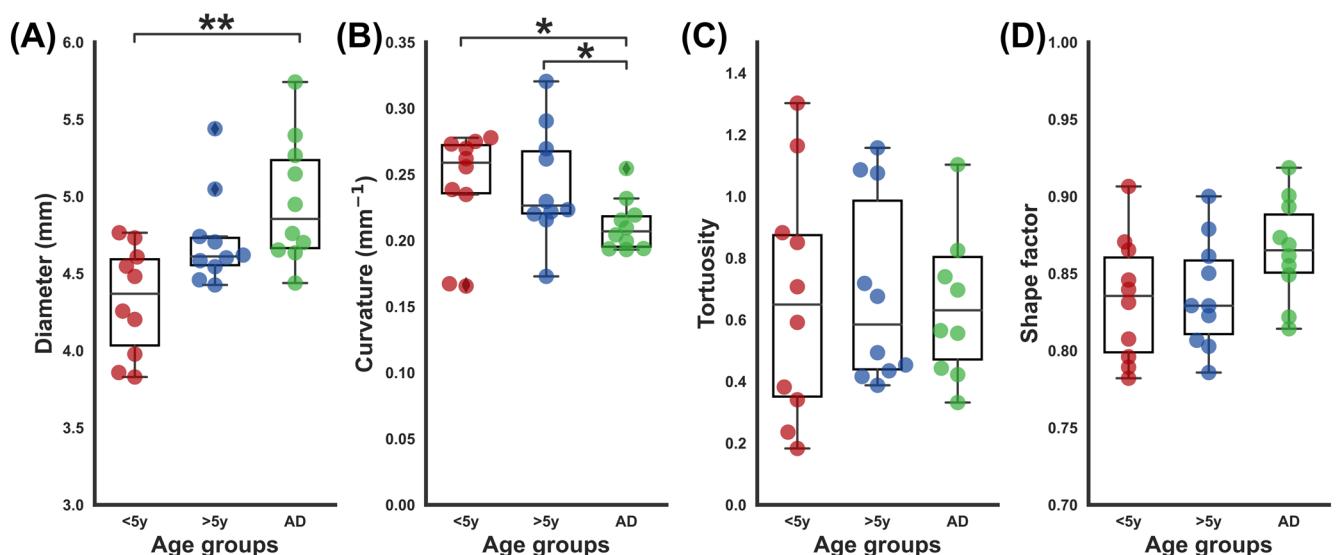


FIGURE 2 | Comparison of internal carotid artery geometrical features between age groups. Geometrical quantities of interest were analyzed for all reconstructed 3D models at the ICA siphon: Diameter (A), curvature (B), tortuosity (C), shape factor (D). Statistical analysis with Mann–Whitney U test: * $p \leq 0.05$, ** $p < 0.01$. Significant geometrical differences between young children (<5 years) and adults are revealed: young children tend to have smaller diameters, larger curvature, and more elliptical cross-section. <5 years: children under 5 years; >5 years: children aged 5 to 18 years; AD: adults. [Color figure can be viewed at wileyonlinelibrary.com]

4 | Discussion

A key finding of this study is that anemia does not fully account for the elevated intracranial arterial velocities observed in SCD

patients. Cerebral blood flow is known to be higher in early childhood due to the metabolic demands of brain growth [18], and is even more pronounced in the SCD population, which exhibits higher cardiac output due to chronic anemia and oxygen

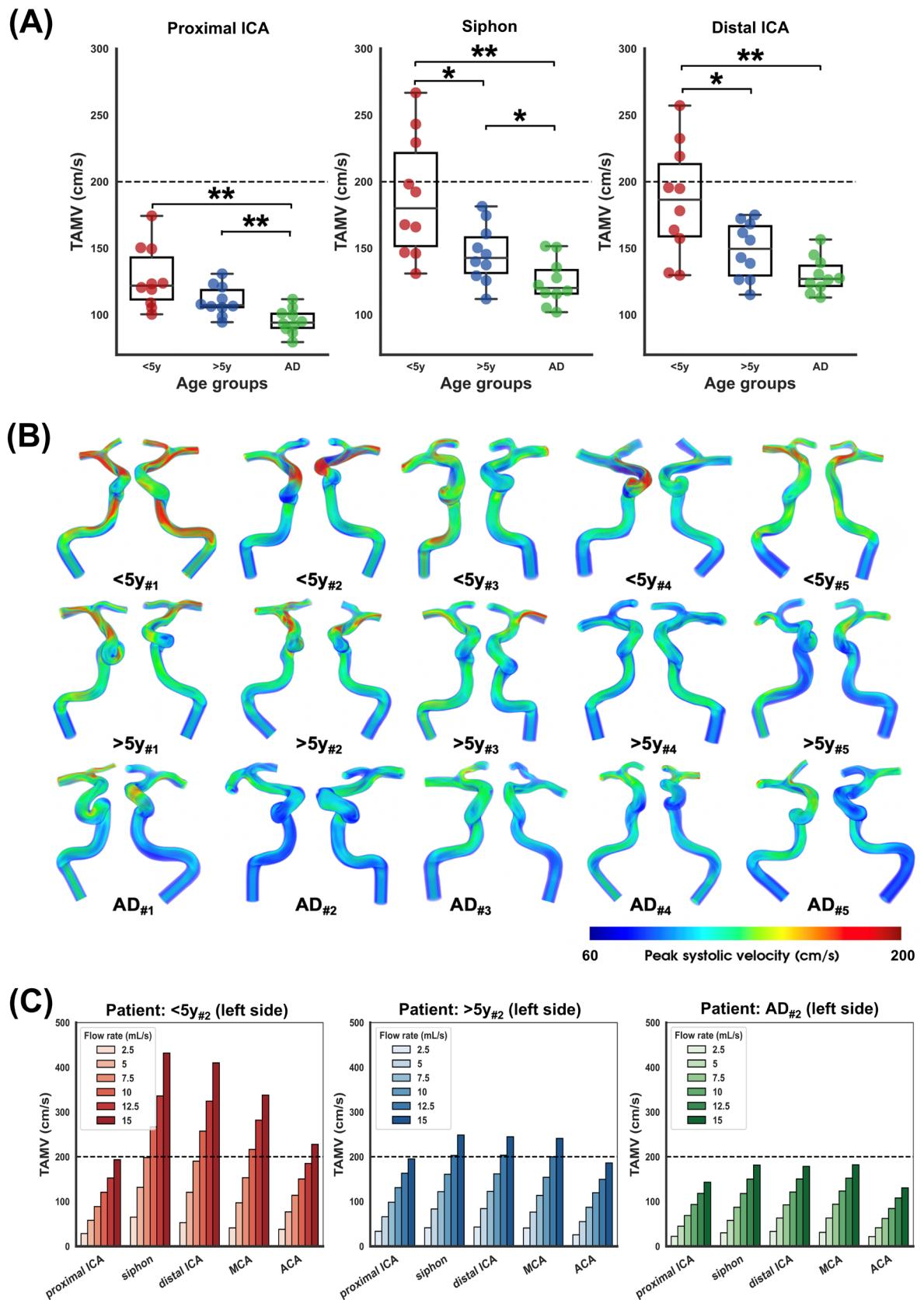


FIGURE 3 | Legend on next page.

FIGURE 3 | Intracranial velocities comparison between age groups. (A) TAMV comparison between age groups in the proximal ICA, siphon, and distal ICA regions, for 10 mL/s inlet mean flow rate. The horizontal dotted line represents the critical TAMV threshold of 200 cm/s. <5 years group patients reach significantly higher TAMV values compared to other age groups under the same flow rate. (B) Velocity magnitude at peak systole for 10 mL/s inlet mean flow rate for all patients (right and left ICA, respectively). High blood velocities are mainly observed in pediatric patients, and most often in the distal part of the ICA. (C) TAMV values for different inlet flow rates ranging from 2.5 to 15 mL/s in one representative patient for each age group. The horizontal dotted line represents the critical TAMV threshold of 200 cm/s. <5 years group patients tend to reach pathological velocities under lower flow rates compared to older patients. Adults never exceed the risk threshold under physiologically admissible flow rates (7.5–10 mL/s). Results for all patients are provided in Figure S5. Statistical analysis with Mann–Whitney U test: * $p \leq 0.05$, ** $p < 0.01$. <5 years: children under 5 years; >5 years: children aged 5 to 18 years; AD: adults; ACA: anterior cerebral arteries; ICA: internal carotid arteries; MCA: middle cerebral arteries; TAMV: time-averaged maximum velocity. [Color figure can be viewed at wileyonlinelibrary.com]

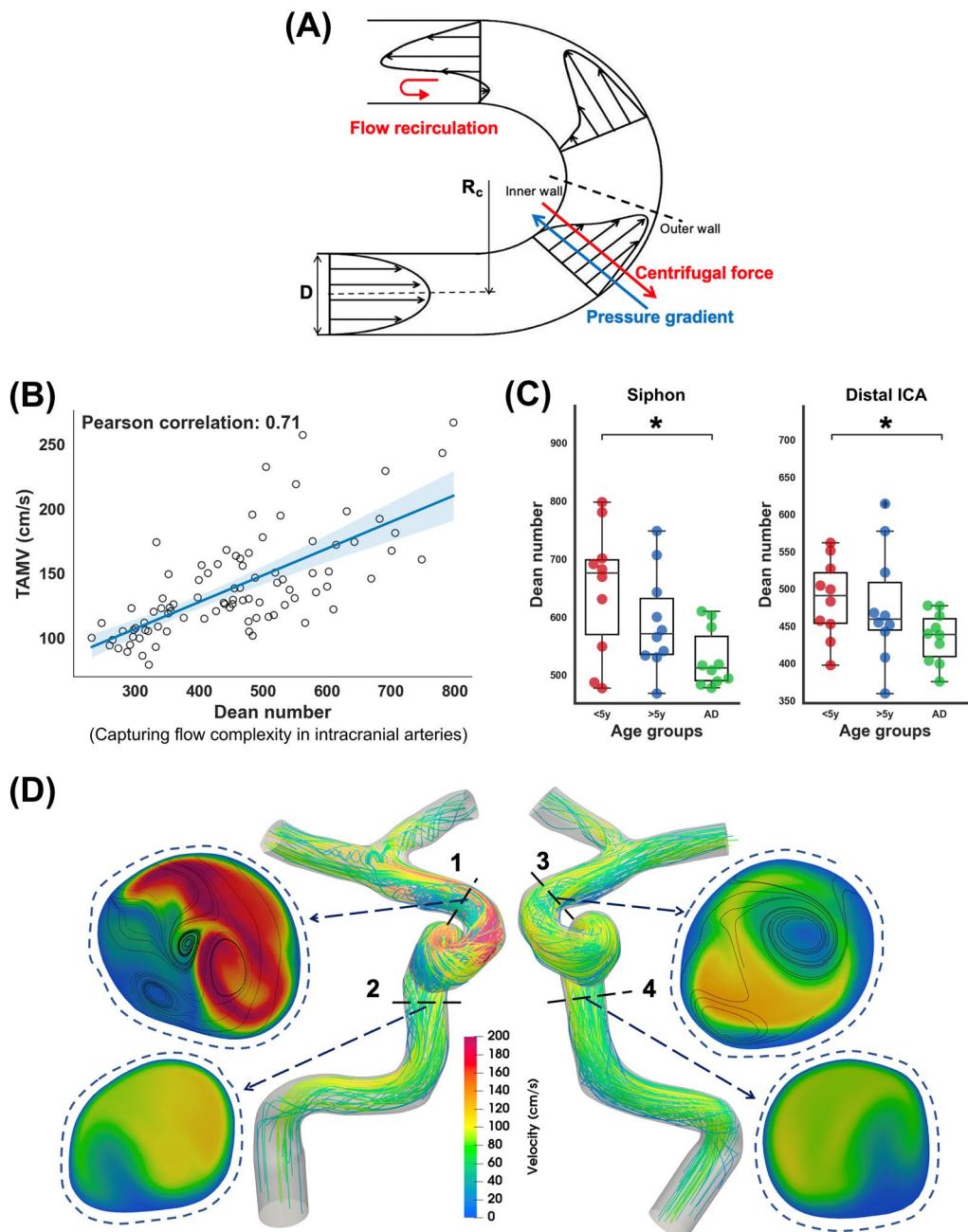


FIGURE 4 | Correlation of TAMV with flow complexity in ICA regions across all age groups. (A) Main effects of curvature on axial flow acceleration and vortex formation. This sub-figure was inspired by Fung's work [17]. (B) Correlation of TAMV with flow complexity (illustrated by Dean number) in ICA regions across all age groups at a mean inlet flow rate of 10 mL/s. (C) Dean number comparison between age groups. (D) Simulation results for a pediatric patient with asymmetric blood flow acceleration between left and right ICA under a flow rate of 10 mL/s. (1–4) Velocity patterns for different Dean numbers at four cross-sectional areas at peak systole. Black streamlines in the cross-sectional areas represent the secondary flow vortices. Statistical analysis with Mann–Whitney U test: * $p \leq 0.05$, ** $p < 0.01$. <5 years: children under 5 years; >5 years: children aged 5 to 18 years; AD: adults; TAMV: time-averaged maximum velocity; D: vessel diameter; R_c : curvature radius. [Color figure can be viewed at wileyonlinelibrary.com]

transport abnormalities associated with the disease [19]. Prior studies have suggested that the elevated cardiac output resulting from both brain growth and the severity of anemia is the primary driver of accelerated intracranial blood velocities in young SCD patients. However, in our cohort, although we observed a strong correlation between hemoglobin levels and intracranial arterial velocities in children over 5 years old, this association was absent in children under five, the very age group in which CV stenosis typically develops. Furthermore, for the same inlet blood flow, TAMV values were significantly higher in children under 5 years old compared to older age groups. Young children tend to reach pathological velocities at lower flow rates (and thus lower cardiac outputs), while adults consistently remained below risk thresholds even at very high flow rates. This finding suggests that anemia is not the sole explanation for elevated intracranial velocities in young SCD patients and that other factors likely play a crucial role. While classical vascular pathology and other SCD complications related to hemolytic anemia (such as pulmonary arterial hypertension and SCD nephropathy) typically manifest with aging [20–23], SCD-related CV differs from these other conditions as it occurs very early in childhood, probably due to the cumulative effects of high flow and vessel geometry.

Indeed, another major finding of this study is the pivotal role of vascular geometry. Our in silico modeling revealed that the combination of smaller vessel diameter and increased curvature in pediatric patients creates a geometric environment that facilitates blood flow acceleration. This is particularly evident in the carotid siphon, where our simulations showed that even at physiologically acceptable flow rates, young children reached critical TAMV thresholds. While higher velocities in children might logically be attributed to the reduced caliber of their arteries, our analysis shows that arterial diameter is not the only morphological parameter at play. Curvature emerged as a major contributor to blood flow acceleration. The tortuous nature of the siphon region, which is not symmetrical in an individual, leads to blood flow acceleration. It may explain unilateral acceleration and lesions observed in some SCD patients, as shown in our previous works, in which approximately 50% of patients exhibited arterial impairment or stenosis on only one side of the ICA and cerebral arteries [24]. However, curvature alone does not fully explain the observed high velocities. Torsion, as an indication of the helical nature of the artery, was investigated by Kao et al. based on computational fluid dynamics simulations in curved pipes [25]. The authors proposed that large torsion could break the symmetry of the vortices into asymmetric ones, explaining flow distortions (asymmetric vortices) and multidirectional shear in the distal ICA region. Even though we did not observe a statistical difference in the mean values of torsion between age groups, torsion may influence local flow pattern on a patient-specific basis, leading to multidirectional velocity temporal gradient and shear. The arterial elliptical shape may also play a role in stenosis formation. Based on the mathematical solution of the simplest flow in a straight conduit, circular arteries (shape factor close to 1) are more efficient in delivering blood flow, with a larger maximum value of blood velocity than more elliptical shapes (shape factor < 1) [26]. Interestingly, a more elliptical arterial shape was observed more frequently in pediatric SCD patients. A more elliptical shape lowers the TAMV, contrarily to the other geometrical parameters studied so far. These opposing effects may account for inter-patient variability. These insights into vascular

morphology not only highlight the mechanical conditions favoring flow acceleration but also raise important questions about the consequences of such hemodynamic alterations.

The third key finding of this study is the strong correlation between increased velocities in intracranial arteries and complex flow patterns, a phenomenon often referred to as turbulence though this term is not strictly accurate. By leveraging advanced in silico modeling, we propose a mechanistic explanation based on the cumulative effects of high flow and vessel geometry, suggesting that flow disturbances may contribute to endothelial damage and promote the development of cerebral vasculopathy. While the exact mechanobiological mechanism of stenosis formation remains unclear, their onset location is generally known to be at the level of the carotid bifurcation [27], and attributed to hemodynamic changes related to this bifurcation [28]. Our work confirms that the highest velocities are recorded at the carotid bifurcation in adults and older children (≥ 5 years). In contrast, in some younger children, it seems that the main hemodynamic events occur slightly upstream, at the carotid siphon, where the highest arterial perfusion rates are recorded. Since the Dean number is correlated with the Reynolds number—a proxy for flow complexity—it can be assumed that the carotid siphon in young children with SCD is an area of very high velocity and pronounced hemorheological disturbances.

Several limitations should be considered when interpreting our findings. First, our in silico model is based on certain assumptions, such as Newtonian fluid behavior and rigid arterial walls. These assumptions may not fully capture the complex blood rheological properties in SCD patients or the arterial wall dynamic behavior; however, we do not expect the main conclusions of this work to be affected. Second, our sample size for the geometric analysis was relatively small, due to the complex and time-consuming nature of the segmentation and modeling protocol. This may limit the generalizability of our findings, and future studies with larger cohorts are needed to confirm these results. Third, our study focused primarily on the geometric and hemodynamic factors contributing to elevated velocities and did not fully explore the role of other potential factors, such as inflammation, endothelial dysfunction, or genetic modifiers.

Despite these limitations, our findings have important clinical implications for the prevention and treatment of stroke in SCD patients. The blood exchange transfusion program, which is known to reduce the risk of stroke [6], may improve oxygen transport through multiple synergistic mechanisms. First, it elevates hemoglobin levels, thereby reducing cardiac output and subsequent carotid artery inflow. Second, it enhances hemorheological parameters and mitigates hemolytic components, which could have an effect on the vascular wall [29, 30]. However, despite repeated blood exchange transfusions, the risk of developing stenosis by the age of 14 remains high, at around 20% [7]. Currently, allogenic hematopoietic stem cell transplant (HSCT) offers the only potential cure for SCD but is limited by the availability of HLA-matched HSC donors, leading to consider gene therapy as a promising curative treatment [31, 32]. A better understanding of the pathophysiology of CV is crucial to improve treatment strategies and reduce the persistent risk of stroke. To our knowledge, this is the first attempt to explain the disproportionate risk of stroke in pediatric SCD patients compared to adults, using in silico modeling.

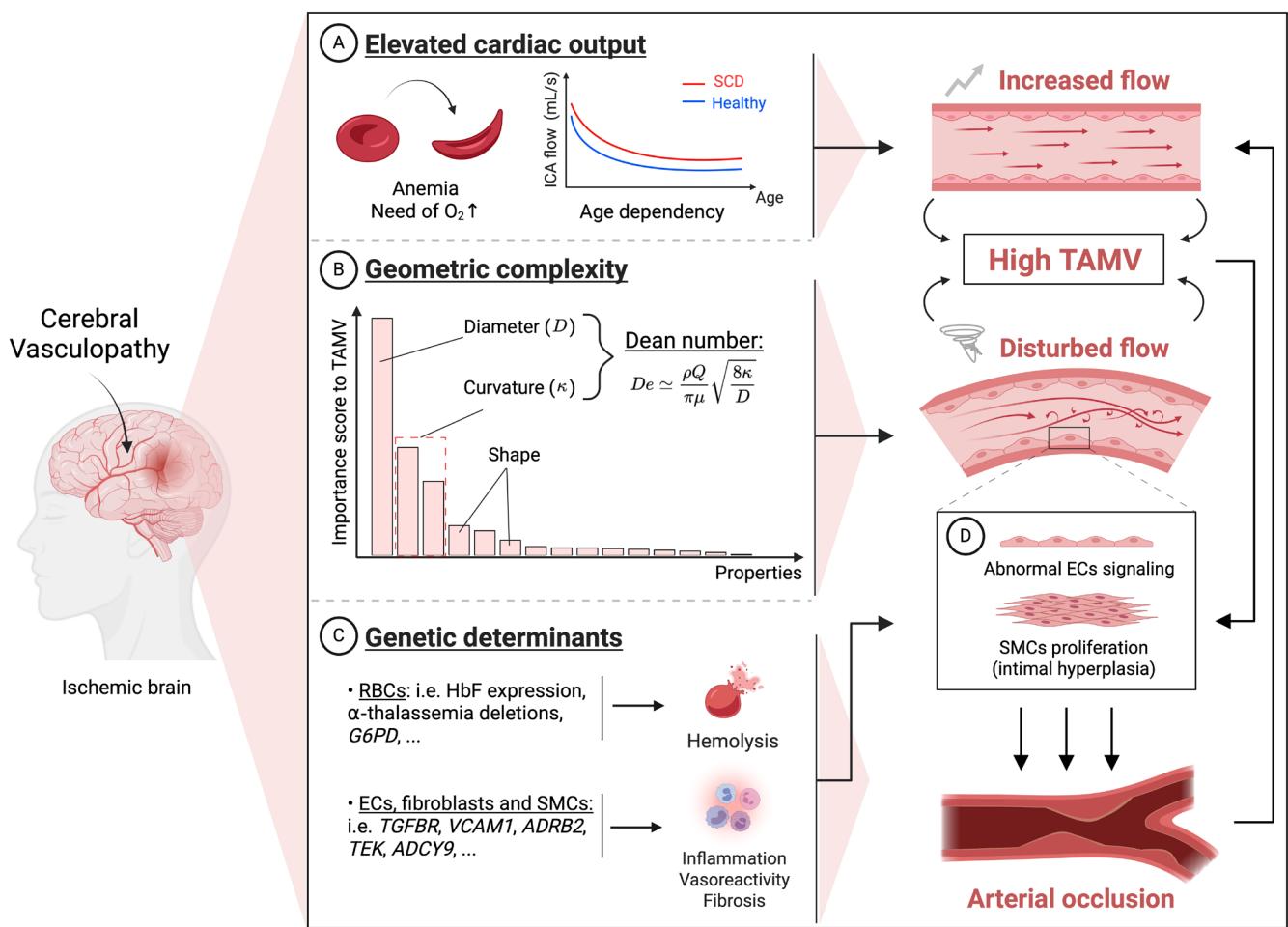


FIGURE 5 | Multistage model for cerebral vasculopathy development. (A) Elevated cardiac output. Due to anemia and erythrocyte membrane abnormalities, SCD patients require higher cardiac output than healthy patients to achieve equivalent cerebral oxygen delivery. This oxygen demand is also age-dependent: younger patients require a higher cerebral blood flow due to brain development and growth. Thus, young SCD patients experience particularly elevated cerebral blood flow rates [12]. (B) Geometric complexity. The importance scores of geometric properties, contributing to time-averaged maximum velocity (TAMV) values computed from a machine learning model under the same input flow rate of 10 mL/s, are ranked in descending order from high to low (Figure S6). Results reveal that maximum velocity is mainly influenced by vessel diameter, curvature, and shape-related factors. Most of these influential parameters are components of the Dean number, a reflection of flow complexity, which correlates with TAMV. In young SCD patients, geometric complexity leads to disrupted flows and complex flow patterns in the siphon and distal portion of the internal carotid artery. These disturbances may lead to platelet activation and endothelial damage. (C) Genetic determinants. Several genetic polymorphisms have been shown to increase the risk of stroke in SCD: at the level of red blood cells by promoting hemolysis, and at the vascular level by disrupting the regulation of inflammation, fibrosis and vasoreactivity in particular. (D) The genetic background, coupled with high TAMV resulting from high cardiac output and geometric complexity, could affect endothelial signaling, myofibroblast and smooth muscle cell proliferation, fibrosis, and platelet degranulation. The end result is intimal stenosis/occlusion leading to cerebral vasculopathy in SCD patients. In addition, arterial occlusion contributes to cerebral hypoperfusion. [Color figure can be viewed at wileyonlinelibrary.com]

The fluid mechanics approach used herein could offer valuable insights in future biological investigations. It is well-accepted that the parietal reaction responsible for CV in SCD is smooth muscle cell proliferation [33], modulated by endothelial cells (ECs), which are the key cellular components of the arterial wall lesions that are preferentially located at branches or bifurcations along the vessel wall, suggesting that local flow dynamics play an important role in lesion development [34]. The accelerated complex flow is expected to impair ECs, leading to inflammation, oxidative stress, and eventually intimal hyperplasia [35–37]. Platelets may also be impacted by disrupted flow, which could lead to platelet degranulation, contributing to the activation of signaling pathways leading to differentiation and proliferation of myofibroblasts, and

fibrosis. In addition, the activation of pathological signaling pathways is further favored by the genetic background found in several studies [38–42]. The interplay between genetic determinants, disturbed flow (resulting from the combination of arterial geometry and elevated cardiac output), and cellular responses warrants further investigation and would be crucial to better understand SCD pathophysiology and CV development.

In conclusion, we propose a multistage, multifactorial model to explain how CV develops in SCD patients, that involves genetic predisposition, vascular lesions due to hemolysis, and hemorheological abnormalities related to blood flow acceleration and vascular geometries (Figure 5). The first stage corresponds to

an unfavorable genetic background which has been extensively studied in the literature [38, 39, 43, 44]. The second stage, which has been the focus of this paper, relates to flow disturbances due to blood flow accelerations, resulting from the combined effects of geometric characteristics and elevated cardiac output. The third stage comprises the cellular response of the endothelial cells, smooth muscle cells, and platelets, as a result of both biological disorders and fluid disturbances [29, 30]. Our work continues with the study of these cellular phenomena, combining mathematical modeling and 3D-printed vessels to study platelet degranulation and the endothelial response to pathological flows and predict the optimal hemoglobin level for a given patient, based on cardiac output, geometry, and viscosity. Finally, these results could serve as a reference for future works in the mechanobiology of SCD and even represent a proof of concept for other pathologies.

Author Contributions

I.V.-C. and P.B. conceived the study and developed the analysis plan. C.K., K.-A.N.-P., N.B., C.P., and S.V. collected the data. W.L., L.P., and J.-F.G. developed the simulation workflow, and W.L. and L.P. undertook the main analysis. W.L., L.P., and C.K. wrote the first draft of the paper. I.V.-C., P.B., K.-A.N.-P., and S.V. made important critical revisions. All authors have read and approved the final version of the manuscript.

Acknowledgments

We would like to express our sincere appreciation to Valentin Amar and Gabriel Nahas for their early exploration of the simulations in this study, and to Pr. David Calvet (neurologist) and Pr. Myriam Edjiali-Goujon (neuroradiologist) for their valuable advice. Figure 5 was created in BioRender: Liu, W. (2026) <https://BioRender.com/b4p232z>.

Funding

The authors have nothing to report.

Ethics Statement

The trial was designed and conducted in accordance with the International Conference on Harmonization (ICH) E6 Guideline for Good Clinical Practice (GCP) and the principles of the Declaration of Helsinki.

Conflicts of Interest

Disclosure of Pablo Bartolucci: Consultant for ADDMEDICA, NOVARTIS, ROCHE, GBT, Bluebird, EMMAUS, HEMANEXT, AGIOS. Lecture fees for NOVARTIS, ADDMEDICA, JAZZPHARMA. Steering committee for NOVARTIS, ROCHE, ADDMEDICA, PFIZER. Research support from ADDMEDICA, foundation Fabre, NOVARTIS, Bluebird, EMMAUS. Cofounder and CSO of INNOVHEM. The remaining authors declare no conflicts of interest.

Data Availability Statement

For original data, please contact pablo.bartolucci@aphp.fr.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Regression of blood flow velocity on hemoglobin and age by intracranial artery. **Table S2:** Characteristics of the in silico modeling cohort. **Figure S1:** Mesh generation. **Figure S2:** Image-based in silico modeling workflow for patients with SCD. **Figure S3:** Validation of the Newtonian model assumption. **Figure S4:** Torsion comparison between age groups. **Figure S5:** TAMV values over different flow rate (2.5–15 mL/s) in five regions of interest. **Figure S6:** Importance scores of properties contributing to TAMV values. **Video S1:** Simulated velocity for a pediatric patient with asymmetric blood flow.