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1. Introduction

Sickle cell disease (SCD) is the most common inherited blood disorder in the world. It is associated with serious complications such as cerebral vasculopathy (CV). CV is characterized by remodeling of the intracranial carotid arteries (ICA), resulting in stenosis and occlusion that can lead to stroke, most commonly in young patients aged 2 to 5 years. A proven method for screening patients at high risk for stroke is transcranial Doppler. A time-averaged maximum velocity (TAMV) greater than 200 cm/s has been proposed as an effective threshold for identifying patients at highest risk (Adams et al., 1992). However, the causes of these pathological blood flow velocities remain unclear. In this work, hemodynamic metrics obtained from blood flow CFD simulations are investigated to understand the development of arterial luminal narrowing.

2. Methods

Magnetic Resonance Angiography (MRA) images of the ICA with cerebral branches are acquired for 15 patients: 5 patients under the age of 5 (<5 y), 5 patients between the ages of 5 and 18 (5-18 y), and 5 adults. The geometries of both ICA (right and left) along with their terminal branches, the middle carotid artery (MCA) and the anterior carotid artery (ACA), are segmented using the software Materialise Mimics. 3D hemodynamic simulations are conducted with the open-source finite-element code FELiScE (https://gitlab.inria.fr/felisce/felisce). A pulsatile inflow typical of the carotid arteries with a parabolic velocity profile is imposed at the inlet with a mean flow rate of 10 mL/s. 3-element Windkessel models are implemented at the outlets with a flow distribution ratio MCA:ACA = 2:1 derived from Zhu et al. (2015).

Blood flow velocity and pressure are obtained by solving the Navier-Stokes equations. Biomarkers such as shear rate and wall shear stress (WSS) are computed in post-processing using in-house scripts.

Table 1. Mean shear rate in the ICA. The p-values are obtained using a Mann-Whitney U test.

Patients	Mean shear rate±SD (s^{-1})	p-value
<5 y	2211±476	
5-18 y	1630±243	<0.005
Adults	1338±152	<0.001

<5 y: patients younger than 5 years; 5-18 y: patients between 5 and 18 years; SD: Standard Deviation.

3. Results and discussion

The mean shear rate in the ICA and the p-values obtained by statistical analysis with the Mann-Whitney

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U test are reported in Table 1. This non-parametric test is chosen, since the statistic distribution is tabulated in the case of small samples. It is performed on the group of patients younger than 5 years and the other two groups, respectively. Statistically significant differences are found. The highest mean shear rate is observed in the youngest patients, while the lowest corresponds to adults. In our cohort, a larger area (in %) of high mean WSS (i.e., above 400 dyne/cm^2) is reported for children, especially for those <5 y. A longitudinal study case of the left ICA for a patient 5-18 y is presented in Figure 1. In Figure 1(A), two MRA are presented at age X on the right-hand side, and seven years later on the left-hand side. A negative evolution of the stenosis at the bifurcation between the MCA and ACA over the years is observed (red dotted circles in Figure 1(A)). In Figure 1(B), the WSS distribution of this patient at age X is computed at end diastole and peak systole. The siphon and most notably the bifurcation appear as regions associated with high WSS at peak systole. We formulate the hypothesis that the growing stenosis could be due to the high WSS and/or the alternating high/low WSS observed in these locations in the simulations.

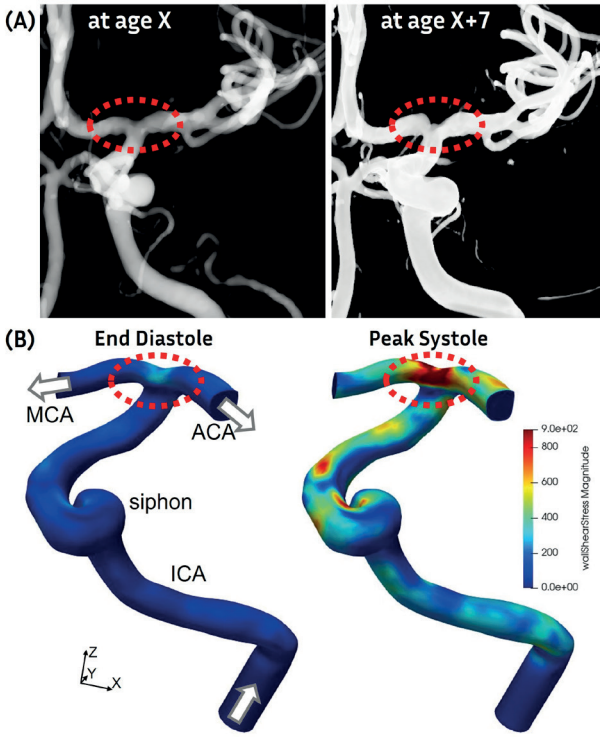

Figure 1. (A) MRA of the same patient (5-18 y) at age X and X+7 years. The stenotic region is circled in red. (B) WSS distribution obtained by simulation on the patient geometry at age X (left ICA).

This preliminary study would benefit from a larger cohort of patients with long-term follow-up as well as healthy control subjects to validate the findings. There are some limitations to our model. Blood was modeled as a Newtonian fluid and the arterial wall considered to be rigid, as the displacement of the ICA wall over a cardiac cycle is usually small. Additionally, although the geometries are patient-specific, the same inflow is imposed for all simulations due to lack of consistent data. Whereas the distal ICA diameter is found to increase with age in our data (on average, in mm: 4.58 for <5 y, 4.90 for 5-18 y, 5.12 for adults), Václavů et al. (2018) reported an age-related decline in flow rate in the ICA for both SCD patients and healthy controls. The inflow chosen in the present study is within the range they reported for SCD patients. Incorporating flow imaging techniques such as 4D flow MRI into the imaging protocol could enhance the approach by giving access to patient-specific velocity fields.

Nevertheless, this work is in agreement with the fact that hemodynamics, particularly shear, is an essential factor in the remodeling of the ICA and the development of stenosis. Another avenue to explore is the relationship between shear, endothelial damage and platelet activation, which may interact in a vicious circle leading to hyperplasia and vessel occlusion (Reda et al., 2022).

4. Conclusions

In this work, the youngest SCD patient group present higher shear rate compared to older patients under the same boundary conditions. Besides, our results suggest that high or/and oscillating high/low WSS might be associated with the growth of stenosis in young SCD patients. This shows that the complexity of the arterial geometry and its evolution at different ages are at play in the development of cerebral vasculopathy. Future work includes verification with more longitudinal cases and experimental validations, as well as platelet simulations.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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