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Impact of Carotid Geometry on Sickle Cell Diseases-related Cerebral Vasculopathy Development

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Introduction

Sickle cell disease (SCD) is the most prevalent monogenic disorder resulting from a mutation in the β -globin gene. Among its severe and multi-system complications, the cerebral vasculopathy (CV) generally occurring during childhood, is responsible for ischemic stroke, making SCD the first etiology of stroke in children and young adults (*Guerrero RM, 2019, Ohene-Frempong K 1998*).

SCD-related overt strokes are typically due to large-artery stenosis of carotid siphon. This stenosis is preceded by a high intracranial arterial velocity on transcranial Doppler (> 200 cm/s) (*Adams RJ 1992*). We hypothesis that the high flow rate and carotid geometry in small SCD children could lead to pathological velocities apparition and promote platelet secretion of pro-fibrotic factors. Thus, a 3D patient-specific vessel model enables to study the physiopathology of CV development. In this study, by developing an *in sillico* and *in vitro* personalized 3D carotid model we aim to evaluate impact of carotid geometry on the apparition of pathological intracranial velocities and the platelet secretion of pro-fibrotic factors.

Materials and methods

Mathematical modelling of internal carotid and vascular flow

The internal carotid artery (ICA) with its terminal branches, anterior cerebral arterial (ACA) and middle cerebral arterial (MCA), was segmented from magnetic resonance angiography images for 4 SCD children < 5 years old (UF), 3 SCD children > 5 years old (OF) and 1 SCD adult (AD) on both sides. Blood flow was modelled using the 3D Navier-Stokes equations, assuming that blood is an incompressible Newtonian fluid. Pulsatile flow was assigned as an inlet boundary condition with mean flow rates varying from 5 to 15 mL/s which reflect the range of flow rates observed in SCD patients. TMMV and Dean number were calculated over five regions of interest, as shown in Fig 1A.

3D printing internal carotid

Segmented internal carotid arteries of an UF and an AD SCD patient were printed using stereolithography 3D printing.

Flow experiments in 3D printed carotid with platelet concentrates

Fresh apheresis platelet concentrates (APC) from 5 healthy donors were perfused in flow system containing either 3D-printed UF or AD carotid at either low or high flow (8 ml/s or 16 ml/s respectively) for 30 minutes. Platelet secretion of soluble CD62P (sCD62P), TGF- β , and TSP-1 at 5 min, 15 and 30 min in the supernatants was measured by ELISA.

Results and discussions

Mathematical modelling of internal carotid and vascular blood flow

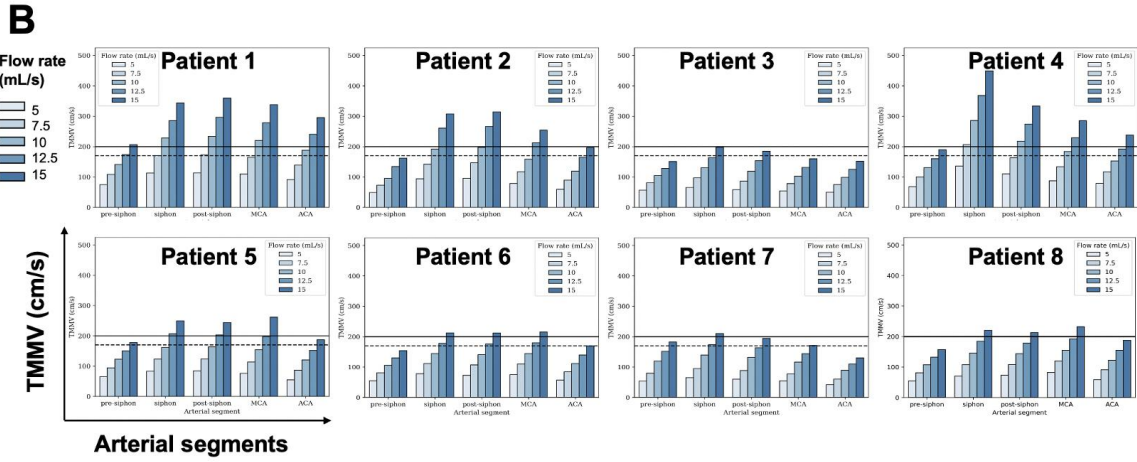
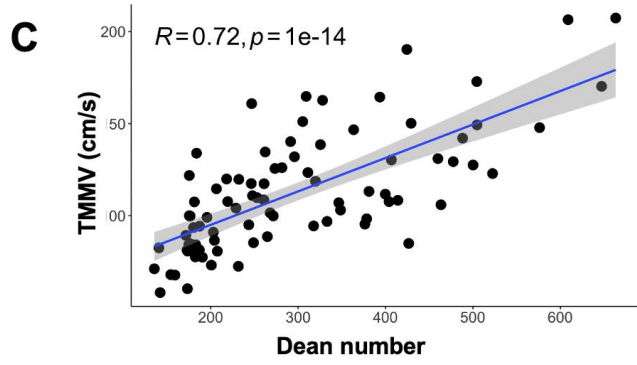
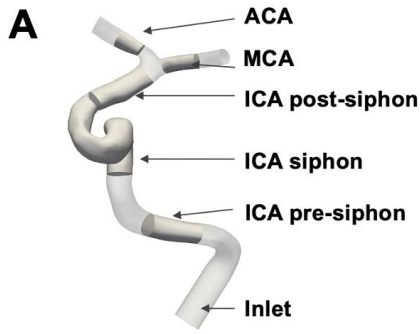
Simulation results show that for any inlet flow rate from 5 to 15 ml/s, the TMMV calculated in younger SCD children tend to be higher than in older patients. Consequently, most UF patients reach pathological TMMV (>200 m/s) at lower inlet flow rates compared to older patients (Fig 1B). The pathological TMMV seem to appear firstly and mostly in the carotid siphon or post-siphon regions (Fig 1B). TMMV shows significant correlation with Dean number ($R = 0.72$, p -value= $1e-14$), as shown in Fig 1C, indicating high flow rate, large curvature and small cross-sectional area of cerebral arteries are closely linked with high TMMV.

Platelet secretion of soluble factors in 3D-printed carotid

The high flow induces an important platelet secretion of the TGF- β , a pro-fibrotic factor with increasing trend in UF than in AD carotid and in a time dependent manner (Fig 1D). In contrast, compared to resting condition, a similar sCD62P level is observed in either AD or UF carotid at low and high flow suggesting the absence of platelet activation in flow conditions, leading to a negligible platelet release of TSP-1, an anti-angiogenic and major endogenous activator of TGF- β . These results suggest that UF carotid geometry could promote platelet secretion of TGF β which is accentuated by high TMMV independently with platelet activation.

Conclusions and perspectives

This study performed in a 3D personalized carotid model has demonstrated that at high flow which are generally observed in UF SCD patients, these patients are more likely to reach the pathological intracranial arterial velocities and the platelet secretion of pro-fibrotic factors compared to AD patients, leading to their high risk of stroke. The measurement of other platelet factors and the evaluation of geometrical features such as diameter, tortuosity and curvature in stenosis formation are in progress. These results could allow to explain the CV development in SCD.



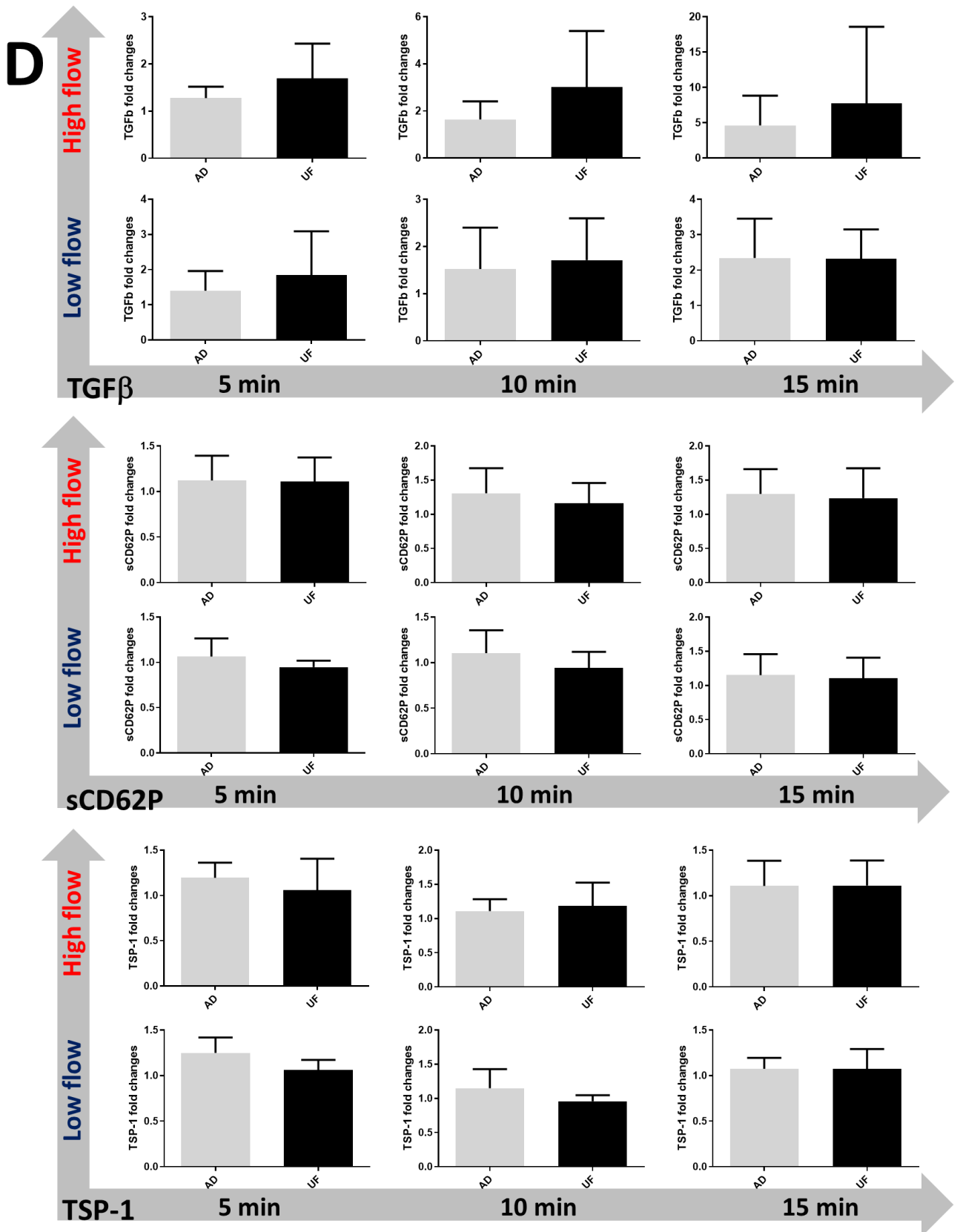


Figure 1: Experiments in 3D personalized carotid model (A-C. *In sillico* model; D. 3D-printed carotid model)

- A. 3D personalized model with its flow inlet and 5 regions of interest (darker grey) for calculation of TMMV and Dean number.**
- B. TMMV calculated in 8 patients (4 UF, 3 OF and 1 AD) over five regions of interest:** Patient 1-8 is sorted by age: 3y2m, 4y1m, 4y2m, 4y8m, 5y5m, 7y11m, 11y3m and 23y respectively.
- C. Correlation between TMMV and Dean number for all patients for a mean flow rate of 5 mL/s.**
- D. Platelet secretion of TGF β , soluble CD62P and TSP-1 in 3D-printed carotid models under flow condition.** Fresh apheresis platelet concentrates (APC) from 5 healthy donors were perfused in flow system containing either 3D-printed AD or UF carotid at either low or high flow (8 ml/s or 16 ml/s respectively) for 30 minutes. Platelet secretion of TGF β , soluble CD62P and TSP at 5 min, 15 and 30 min in the supernatants was measured by ELISA. The fold changes of each factor are computed as the ratio of concentration between the indicated and the resting condition (before perfusion). Data from 5 independent experiments. Bars represent the mean \pm SD. The differences are not significant (Wilcoxon matched-pairs signed rank test $p > 0.05$)