Velocity and wall shear stress in the Circle of Willis in Sickle Cell Disease using 4D flow MRI

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Introduction: Wall shear stress (WSS) is the tangential force exerted by the flowing blood on the endothelial wall and is dependent on the dynamic viscosity of blood. Viscosity is dependent on hematocrit (Hct), which is abnormally low in sickle cell disease (SCD). Endothelial dysfunction in SCD could be related to low WSS but this hasn't been studied in the circle of willis (CoW), whereas low WSS in carotid has been shown to be atheroprotective[1]. SCD is associated with increased risk for stroke and vasculopathy[2] and therefore serves as an interesting patient population to investigate in relation to WSS. In this pilot study, we explore the feasibility of 4D flow MRI and WSS estimation in the CoW, and the Middle Cerebral Artery (MCA). We hypothesize that mean velocity and MCA diameter will be higher in the sickle cell patients, while we expect WSS to be lower, according to previous allusions to atherogenic mechanisms attributed to low WSS with vasodilation[2]. On the other hand one might expect WSS to also increase, since, when velocity increases, so too should WSS[3].

Methods: 9 patients diagnosed with SCD HbSS or HbSβ^0-thalassemia genotype (aged 13±2 years, range 8-15 years), and 5 age matched controls (aged 16±4, P=0.07, Wilcoxon rank sum test, P<0.05 was considered significant), were recruited from two Dutch centers (Emma Children's Hospital, Amsterdam, and Sophia Children's Hospital, Rotterdam) and were scanned with a 3.0 Tesla Philips Intera clinical scanner (Philips Healthcare, Best, The Netherlands) with an 8-channel head coil. The MRI protocol comprised a 4D flow MRI sequence over 4 heart phases, imaged at the level of the CoW, based on a prior angiogram. Scan parameters were: TE/TR 3.2/6.5ms, flip angle 20°, pixel size 0.5 x 0.5 x 0.5mm^3, SENSE 2, venc 100 cm/sec, scan time 5 min. Because controls were part of another study, they underwent a slightly different protocol with the following differences**:** number of heart phases 2, pixel size 0.45 x 0.45 x 0.5mm^3, flip angle 15°, SENSE 3. The CoW was segmented from phase contrast magnitude images using a commercial software package (Mimics, Materialise, Leuven). The MCAs were manually segmented in Matlab (Mathworks, Natick, NC). The velocity fields in the Circle of Willis and the MCAs were filtered with a 3x3x3 voxels median filter. WSS was calculated using the algorithm based on Potters et al.[4]with an added module for automatic MCA diameter extraction. The mean velocity and WSS were calculated for each measured cardiac time frame and were subsequently averaged over the frames. Hct was measured from blood drawn from an antecubital vein. Viscosity was calculated from Hct using[5]: $\eta = 1.24e^{0.02471Hct}$. A standard Hct value of 38% was assumed for controls[6]. A Wilcoxon rank sum test was used to test for significant differences in mean velocity, mean WSS and MCA diameter between patients and controls; P<0.05 was considered significant.

Table 1. *Mean velocity, mean WSS and diameter in the left and right middle cerebral artery for SCD patients compared to controls.*

		Controls	Patients	*P**
Mean velocity (m/s)	LMCA	0.47±0.07	0.53±0.08	0.30
	RMCA	0.46±0.06	0.52±0.05	0.06
Mean WSS (Pa)	LMCA	5.0±0.59	3.3±0.62	<0.001
	RMCA	5.1±0.65	3.1±0.44	<0.001
Diameter (mm)	LMCA	2.1±0.45	2.8±0.29	0.02
	RMCA	2.0±0.10	2.9±0.19	<0.001

*LMCA/RMCA=left/right middle cerebral artery *Wilcoxon rank sum test, P<0.05 considered significant*

Results: Hct values were 24±3.9% (range: 18 – 30 %) and mean viscosity was 0.0022 Pa.s for the patients. Table 1 shows the mean velocity, WSS and diameter in the MCA, indicating a trend towards an increased mean velocity in patients compared with controls. It was found that WSS was significantly lower and that MCA vessel diameter was significantly larger in SCD patients (Table 1). In figure 1, velocity in the entire circle of Willis and WSS in the left and right MCA are shown for a healthy volunteer (a) and a patient (b), respectively. It can be seen that the WSS is lower for the SCD patient compared to the control.

Discussion/Conclusion: Our findings were threefold: **A)** the velocity was not significantly higher in patients, but showed a trend towards increased velocity compared with controls. **B)** The measurement of WSS was feasible in the MCA and showed a significantly lower WSS than in controls. Strikingly, these significant differences were apparent in a small patient sample of 9 and only 5 controls. **C)** The diameter of the MCA was significantly larger in patients, indicating vasodilation compared with controls. These measurements should be repeated in a larger patient and control population. For example, a limitation of the current experiment is the low temporal resolution (2 heart phases were averaged in controls, and 4 in the patient group). Moreover, we cannot rule out that WSS would be different if the viscosity was measured directly. Despite a slightly higher velocity in the MCA for sickle cell patients, lower WSS was found, which may induce vascular inflammation. In conclusion, we show that WSS measurements are feasible in the circle of Willis and that with careful consideration of confounding variables 4D flow MRI can be used to measure velocity and WSS in SCD in a short scan.

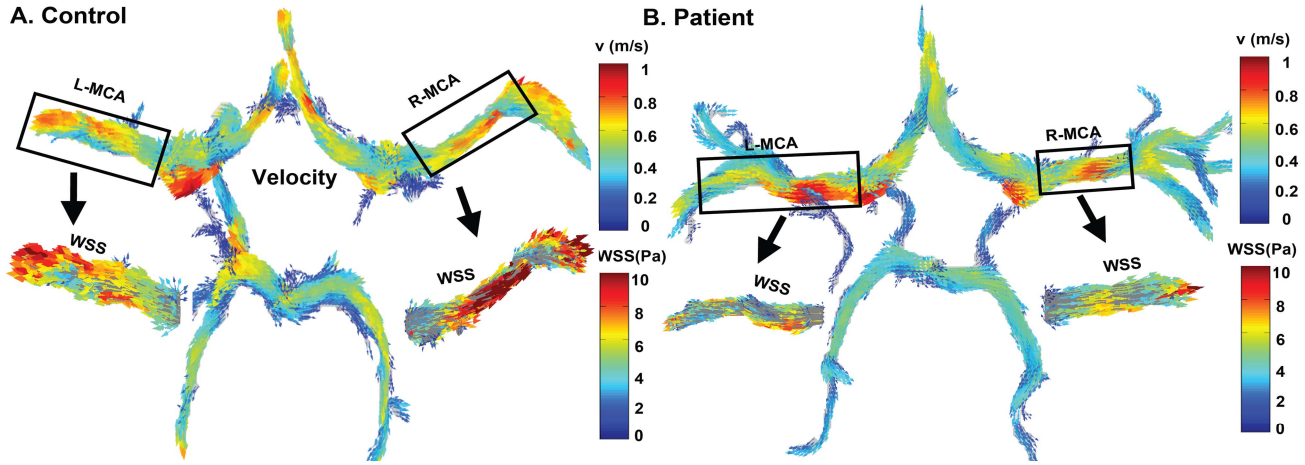

Fig. 1. *Velocity in the Circle of Willis of* ***(a)*** *a 10-year old healthy control, and* ***(b)*** *a 15-year old sickle cell patient. Insets show WSS in the left and right MCA*

References: *[1]Dai et al.Proc.Natl.Sci.USA, 2004, [2]Adams Arch Neur. 2007, [3]Belhassen et al. Blood 2001, [4]Potters et al.2013 JMRI, [5]Zingg et al. Can.J.Phys.Pharm.1970, [6]Robins& Blum, Am. J. Hem.2007*