Using MR-measured cerebral blood flow to assess stroke risk in pediatric sickle cell patients

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Purpose. The purpose of this presentation is to highlight the potential for using phase contrast MR (PCMR) to quantify cerebral blood flow to determine stroke risk in pediatric sickle cell disease patients. In the US alone, approximately two million people (1 in 12 African-Americans) carry the sickle cell trait, and 72,000 people are homozygous for the sickle cell gene (HbSS) and are said to have sickle cell anemia [1]. There is a 10-25% chance of cerebrovascular accident (CVA) (e.g. infarctive or ischemic stroke, or transient ischemic attack (TIA)) in a pediatric HbSS patient who does not receive preventative therapy (e.g. blood transfusion), but the etiology of stroke development in these patients is not completely understood [2-5]. Evidence of cerebrovascular damage was seen in 24% of HbSS patients, and cognitive deficiencies due to "silent" damage (e.g. infarct/ischemia, hypoxia without clinical stroke) are thought to affect five to nine times the number of patients as clinical stroke [3,6]. Because of the prevalence of stroke in pediatric HbSS patient populations and because of the devastating effects of these CVA on the physical, cognitive, and developmental health of the child, standard of care is to identify children "at risk" of stroke and place them on prophylactic transfusion therapy, with the goal of lowering sickle hemoglobin (Hb) concentration [2,7]. Risk factors include previous CVA and abnormally "high" middle cerebral artery (MCA) or internal carotid artery (ICA) velocities [5,7,8]. In addition, brain lesion severity (an indicator of impaired brain function) detected by MR was shown to inversely correlate with total blood flow through the proximal internal carotid and basilar arteries, and large arteries (e.g., the ICA and its branches) are implicated in both stroke and TIA [2,6,9-11]. This demonstrates the importance of accurately measuring cerebral blood flow in these patients, for which PCMR is singularly well suited.

Outline of Content. Transcranial Doppler- (TCD-) measured peak or time-averaged mean velocities are used as criteria for placing pediatric HbSS patients on transfusion [2,7]. These "high" velocities are often considered indicative of stenosis; however, from a fluid mechanics standpoint, high velocities do not conclusively demonstrate local stenoses, nor do they predict future occlusions. High peak arterial velocity may be observed for a variety of reasons. In patients *with* stenotic lesions, high peak velocities will be observed at the location of stenosis (i.e. measuring velocity in the same vessel away from the stenosis would show lower peak velocities). In these patients both PCMR and TCD measurements would reflect the increase in velocity; however, only PCMR data would measure the entire velocity distribution. In patients *without* stenotic lesions, high peak velocities could occur for two major reasons: (1) a true increase in flow (e.g. kg/s), or (2) the actual flow (volumetric or mass flow) stays the same, but the velocity profile is skewed (i.e. due to a curve, a bifurcation, or a non-pathological narrowing of the vessel), which would cause a false high *local* peak velocity. A true increase in flow (and accompanying increase in velocity) would be detected by both PCMR and TCD measurements. PCMR data would accurately reflect the condition of constant flow and increased local peak velocity (i.e. due to a curve in the vessel); however, TCD measurements would indicate the increased peak velocity, but would not reflect the constant flow. Thus, TCD-based interpretation of flow conditions would lead to erroneous risk assessment for a patient.

The temporal resolution of TCD is superior to that of PCMR, but current diagnostic criteria are based on average or peak velocity values. In addition, physical limitations hamper TCD measurements. In adults, transcranial color Doppler (TCCD) imaging and PCMR (1.5 T) measurements in extracranial vessels showed better correlation than those in intracranial vessels, due in part to the influence of temporal bone on TCCD measurements [12]. This study showed a lack of correlation between TCCD and PCMR measurements of peak systolic flow for the MCA, the anterior cerebral artery, and the posterior cerebral artery; however, TCCD correlated well with PCMR flow measurements for the ICA, the basilar artery, and the vertebral artery.

Measuring cerebral blood flow in healthy adult subjects, PCMR underestimates peak velocities compared to TCCD [12]. Peak velocity measurements will be greater via TCD than PCMR because of the nature of data acquisition. For a given voxel PCMR yields velocity measurements averaged (1) temporally over a number of discrete time points in the cardiac cycle, and (2) spatially over the voxel. However, *in vitro* studies of unsteady flow determined that 1.5 T PCMR-measured velocities deviated from analytical values by 7.5% of the mean fluid velocity; whereas, TCCD overestimates peak velocity up to 25% [13,14]. Previous *in vitro* studies compared PCMR and Doppler sonography estimations of volumetric flow with peripheral artery waveforms and demonstrated that PCMR flow measurements correlated better with actual flow than did Doppler sonography [15]. In addition, a PCMR-based method for assessing disturbed flow in areas of partial occlusion may provide the capability for measuring flow in stenotic regions [16,17].

Ideally, measurements would be taken at the same location, both in a single subject over time and in different subjects across the population. TCD does not allow a global representation of the vessels; consequently, measurement locations are prone to inter- and intra-subject variability and identification of vessels can be challenging. Locating major cerebral vessels is more successful using PCMR than with TCD [18,19]. Given cerebral artery branching, tortuosity, and geometrical variation among subjects, changing measurement location would influence velocity measurement under steady flow—this variability would be exacerbated under physiologic pulsatile flow. In both imaging modalities a major source of error can be angle of acquisition. With Doppler measurements both intraprobe variation and angle of insonation (with respect to the vessel) introduce measurement error [12,14]. Zhao *et al.* (2000) determined that orientating the PCMR slice such that the through-plane velocity aligns with vessel direction decreases flow rate estimation error [20]. Prior to PCMR measurements an MRA scan can be used to describe the location of the cerebrovascular branches in three-dimensional space; therefore, measurement locations can be chosen in reference to anatomical landmarks. Using MR and PCMR allows the operator to define repeatable measurement locations—both intra- and inter- subject.

Summary. PCMR is a non-invasive method of quantifying temporally and spatially varying arterial velocities and blood flow. Accurate measurement of cerebral blood flow is of vital importance in pediatric sickle cell patients, and the use of PCMR in conjunction with current methods could greatly improve flow quantification and stroke risk assessment.

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