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Investigation of Cerebral Hemodynamics and Collateralization in Asymptomatic Carotid Stenoses

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Abstract— **Stroke is the second leading cause of death in the world, and one of the major causes of disability. Approximately 30% of ischemic strokes are due to plaque rupture in the carotid arteries. The most popular diagnostic method uses Doppler ultrasound to find the percent stenosis. However, other factors, such as the hemodynamics around the plaque may play a larger role in identifying the risk of plaque rupture. It has been shown previously in simulations that non-collateral flow in the circle of Willis (COW) could cause an increase of the intraluminal velocity around carotid plaque. This added strain may increase the vulnerability of the plaque to rupture. We investigated asymmetries in flow waveforms in the middle cerebral artery (MCA) in asymptomatic patients with carotid artery stenosis. We compared clinical results of velocity waveforms in the MCA, acquired using transcranial Doppler (TCD), with a simple linear simulation model of the intra- and extracranial arterial network to investigate the relationship between contralateral and ipsilateral flow profiles in the MCA for patients with asymptomatic carotid stenosis. In 17 out of 23 patients we found waveforms consistent with those predicted for a collateralized COW, with minimal differences in delay, velocity magnitude and resistivity index. In 6 cases, some unexpected findings were noted, such as large delays for 2 patients ≤ 50% stenosis, and a large velocity difference with low delay for 4 patients. More studies are needed to elucidate the role of incomplete intracranial collateralization on the hemodynamics around carotid plaque and to use imaging of the COW to corroborate our results.**

I. Introduction

As the second leading cause of death, and sixth cause of disability in the world, stroke affects millions of people each year. Approximately 20% to 30% of ischemic strokes are caused by the rupture of atherosclerotic plaque in the carotid artery [1]. The current diagnostic method estimates the degree of stenosis, in the carotid artery, from Doppler ultrasound measurements of peak systolic velocities (PSV). Although this criterion is in common clinical use, it does not provide direct information about the likelihood of plaque rupture. Other factors, such as the hemodynamics around the plaque may play a larger role than the degree of stenosis alone [2,3]. Hemodynamic affects on the plaque is suggested to be a cause of intraplaque hemorrhaging and an increase in the pressure differential between the plaque and lumen, which may lead to increased risk of plaque rupture [4,5].

Before ultrasound, one of the methods for detecting carotid artery occlusive disease was oculoplethysmography (OPG), which measured pressure waveforms of the ophthalmic artery from the eyes [6]. A delay between the pressure waveform arrivals in each eye indicated the presence of carotid artery stenosis on the delayed side. It was later compared to angiography and was shown to have insufficient accuracy [7]. A recent simulation study by Lal *et al.* of the interconnected intracranial and extracranial circulatory system showed that a cause of the pressure waveform arrival delay in OPG could be due to non-collateral intracranial flow in the circle of Willis (COW) [3].

Only about 50% of the world's population have a complete COW, while 45% have one missing or atretic artery in the COW (capable of partial collateral flow), and 5% having two or more missing segments in the COW (incapable of collateral flow) [3, 8]. The hemodynamics in a stenotic carotid artery would be affected by the collateralization in the COW, since it is an interconnected system.

The aim of this work is to investigate whether carotid stenoses are associated with pulse delays between velocity waveforms in the middle cerebral artery (MCA) ipsilateral and contralateral to the stenosis in asyptomatic patients with carotid artery disease. Measurements of MCA velocity waveforms using transcranial Doppler (TCD) were used to provide a more accurate measure of pulse delay due to non-collateral flow in the COW. The measurements from TCD were compared to results from simulations of a circuit model of the COW and its major supply pathways. To the best of our knowledge, this has not been previously investigated in a clinical population.

II. Materials and Methods

A. Participants

This study was conducted at the Veteran Affairs Medical Center in Baltimore, MD following approved procedures. Patients with asymptomatic carotid stenosis were recruited for the study. Eligible participants had asymptomatic carotid stenosis ≥ 50%, which was identified by an imaging modality. Participants were excluded if they had a previous stroke or transient ischemic attack (TIA), severe medical

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illness, carotid occlusion, or if they had been scheduled for carotid revascularization. All patients underwent a carotid duplex exam and bilateral TCD of the MCA. Patient scanning was conducted by an experienced sonographer.

B. Doppler Ultrasound

Each patient underwent two Doppler exams: 1) duplex Doppler of the extracranial carotid arteries, and 2) simultaneous bilateral TCD of the MCAs. The patients first go through a full carotid artery duplex ultrasound exam, which includes measurements of the PSV around carotid plaque. Then bilateral TCD waveforms of MCA velocities were recorded with a 2 MHz single element transducer, using an ST3 Bilateral Transcranial Doppler system in conjunction with a head frame (Marc 600) by Spencer Technologies (Seattle, WA, USA). The system is capable of saving bilateral "raw" quadrature-demodulated in-phase and quadrature-phase (IQ) data for offline analysis.

C. TCD Data Analysis

Each TCD data file consisted of an 8 second long M-mode of the "raw" IQ data acquired at a pulse repetition frequency of 8 kHz bilaterally. MATLAB (Mathworks, Inc., Natick, MA) was used to process the data. MCA velocity spectrogram was calculated using short time Fourier analysis of the IQ M-mode data at the acquisition depth selected by the sonographer during the exam. The delays between the ipsilateral and contralateral MCA velocity spectrograms were measured in MATLAB using two methods: 1) manual measurements, and 2) semi-automatic method for finding the onset of the pulses. The delays were calculated in 4-8 cardiac cycles for each patient.

In the manual method, the velocity and onset were measured at two locations on the waveform: 1) peak systole, and 2) onset of systole. The semi-automatic method was used to measure a specific time instant in each cardiac pulse corresponding to 95% of MCA PSV. A threshold was set to find the onset of the time waveforms taken 5% down from the peak of the signal, and the delays were calculated by comparing these time instants between the ipsilateral and contralateral waveforms. To minimize any bias associated with choice of the signal processing method, the velocity waveforms and delays were also calculated using a conventional autocorrelation-based velocity estimator.

III. Simulation Model

The simulation model used in this study is based on the work by Lal *et al.* [3]. A simple linear circuit model was used to represent the intracranial and extracranial cerebral circulation. The model included a simplified anatomical representation of the connected circulation, a physiological model of hemodynamic flow waveforms, and a fluid mechanical model of pressure drops. The detailed model is described in [3]. In the following sections, we will briefly describe the anatomical and circuit model. The goal of the model is to predict any delays introduced by non-collateral flow in the COW.

A. Anatomical model

The COW is a redundant network of interconnected vessels for assuring collateral flow to the brain in the event that flow is limited in one of the supplying arteries. Flow in the COW is supplied through three arteries, the left and right internal carotid arteries (ICA) and the basilar artery (BA), which is formed by the merging of the left and right vertebral arteries. Most of the blood supply comes from the ICAs. There are three arterial branches from the COW that supply each cranial hemisphere. The branches are the MCA, anterior (ACA), and posterior (PCA) cerebral arteries. The COW has an anterior and a posterior segment, and both are symmetrical between the two hemispheres. The anterior segment is connected to the posterior segment through the posterior communicating artery (PCoA). In the anterior side, the left and right ACA segments in each hemisphere are connected through the anterior communicating artery (ACoA). Any one or a combination of segments in the COW may be atretic or missing. For the model used in this work, the missing segments were both PCoAs and the ACoA.

When two or more segments are missing from the COW then the brain blood supply will not have the potential to develop collateral flow. If the flow in the supplying arteries is normal then adequate supply will remain in all cranial hemispheres. However, in the presence of an ICA stenosis, then the pressure is reduced in the ipsilateral segment of the COW. This will result in an increased velocity in that ICA to maintain normal cranial flow rate.

B. Circuit Model

Our linear circuit model of the system, shown in Fig. 1, consisted of two main components. The first component consists of the extracranial carotid arteries (red dashed box), represented with resistances for the carotid arteries and a left carotid stenosis, R_{CL}, R_{CR}, and R_{SL} respectively.

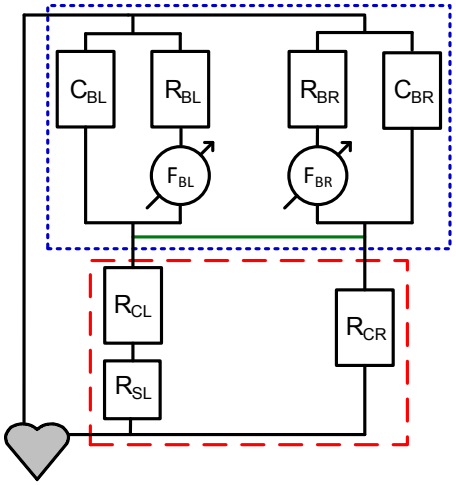

Figure 1. Circuit model of the system consists of two main components. The first component consists of the carotid arteries in the neck (red dashed box), represented with a resistances. The second part is the brain (blue dotted box) consisting of a resistance and a capacitance in parallel.

The second part is the intracranial circulation in the brain (blue dotted box) consisting of a resistance, R_{BL} and R_{BR}, and a capacitance, C_{BL} and C_{BR}, in parallel for the left and right hemispheres respectively. F_{BL} and F_{RL} are the brain flow measurement locations. The green line connecting the

left and right hemispheres provides collateral flow in the system.

In our model, we used the sum of the carotid and brain resistances as 25 mm Hg/(mL/s). The contralateral carotid resistance used was R_{CR} = 2.5 mm Hg/(mL/s), making the brain resistance on that side R_{BR} = 22.5 mm Hg/(mL/s). The additional resistance representing the stenosis was R_{SL} = 7.5 mm Hg/(mL/s). This makes the total carotid artery resistance on the stenotic side of 10 mm Hg/(mL/s), making the brain resistance R_{BL} = 15 mm Hg/(mL/s). The left and right brain capacitances are C_{BL} = C_{BR} = 0.05 mL/mm Hg. Using an aortic pressure waveform with a mean of 100 mm Hg, the brain flow F_{BL} and F_{BR} can be calculated by solving the linear model. In order to predict the MCA velocities, we assumed for simplicity that the brain flow and MCA flow were the same.

IV. Results

A. Simulation results

Simulations were conducted of a carotid artery with a 67% ICA stenosis for two configurations of the COW, complete (collateral flow) and an incomplete (non-collateral flow) circle. The resulting MCA velocity waveforms on the ipsilateral (red dashed line) and contralateral (blue solid line) sides to the stenosis are shown in the top and bottom of Fig. 2. For a complete COW (top of Fig. 2) there was no predicted delay or magnitude change, due to collateral compensation of the flow from the contralateral side.

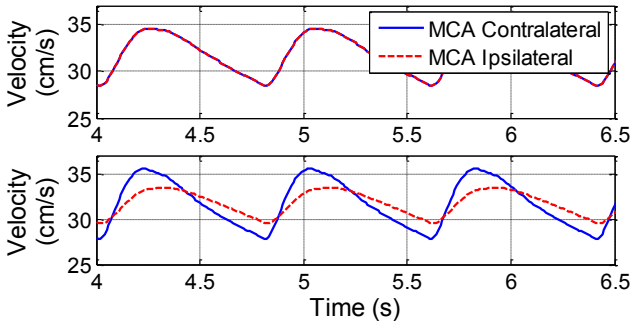

Figure 2. Simulation results of middle cerebral artery (MCA) velocity waveforms on the sides ipsilateral (red dashed line) and contralateral (blue solid line) to a 67% internal carotid artery (ICA) stenosis. The top and bottom plots show velocity waveforms from a circle of Willis with collateral and non-collateral flow respectively.

However, when the COW is incomplete (bottom of Fig. 2), we observed a peak velocity reduction of about 2.12 cm/s between ipsilateral and contralateral flow waveforms. We also observed a delay of 89 ms in peak systole between the ipsilateral and contralateral velocity waveforms. The delay during the onset of systole was 10 ms.

B. TCD Clinical Results

Bilateral data from TCD of MCA velocities from 23 patients was analyzed. 21 patients had simultaneous bilateral measurements, and 2 without simultaneous bilateral measurements were included due to the presence of high ICA PSV. This was done to study the trend of velocity change between the MCA waveforms ipsilateral and contralateral to the stenosis in the range of very high ICA PSV. There were four manually measured values: the delay at two locations 1) peak systole and 2) onset of systole, and the difference in MCA 3) PSV between the ipsilateral and contralateral MCAs. The values were measured for multiple heart cycles (between 4 and 8) in each patient to observe any cycle-to-cycle variability in the measurements. The delay was also measured with our semi-automatic method to confirm our manual measurement findings.

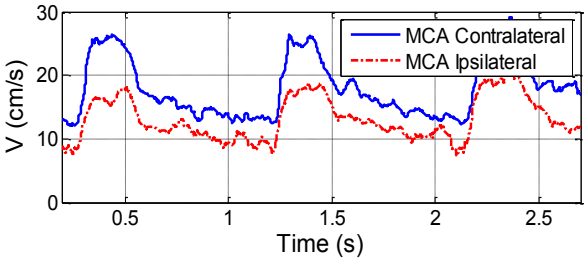

Figure 3. Middle cerebral artery (MCA) velocity waveforms from transcranial Doppler on the sides ipsilateral (red dash-dot line) and contralateral (blue solid line) to an internal carotid artery with stenosis.

Fig. 3 shows the resulting MCA velocity waveforms from the ipsilateral (red dash-dot line) and contralateral (blue line) sides to the stenosis. This velocity was calculated using the autocorrelation method, a mean velocity estimator, with a 68 ms smoothing window. This data is from a patient classified as having 50% - 70% stenosis from duplex ultrasound.

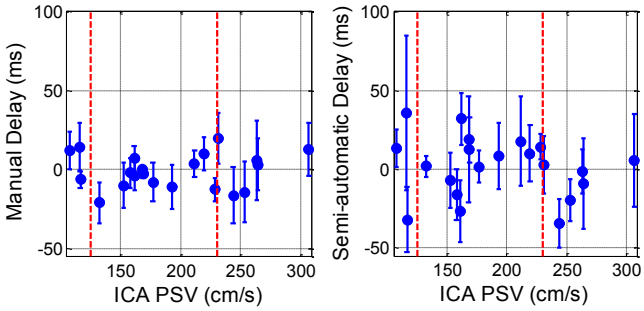

Figure 4. Error bar plots showing the delay between the ipsilateral and contralateral middle cerebral artery (MCA) velocity waveforms from manual (left plot) and semi-automatic (right plot) methods. The vertical red dashed lines are the peak systolic velocities (PSV) cutoff points for 50% (left line) and 70% (right line) internal carotid artery (ICA) stenosis.

Fig. 4 shows error bar plots of the delay during peak systole from the manual (left plot) and semi-automatic method (right plot) vs. the ipsilateral ICA PSV. Each dot represents a patient, and the error bars represent the standard deviation of the measurements between cardiac cycles. The red dashed lines are the duplex ultrasound cutoff ICA PSV for 50% (125 cm/s) and 70% (230 cm/s) stenosis. We observed an approximately consistent trend in delays using both methods, with the semi-automatic method having somewhat larger delays and variance. We also observed an unexpected finding of a relatively high delay for two patients with low ICA PSV. Delays with a similar trend were also observed during onset of systole.

Fig. 5 shows the difference in MCA PSV (ΔV) between the contralateral (V_C) and ipsilateral (V_I) sides to the carotid stenosis ($\Delta V = V_C - V_I$). The variance is much smaller than in the delay measurements. We observed a small increasing trend with increasing ICA PSV, but it was not statistically significant. However, there were 4 cases that had relatively

high asymmetry. One case (bilateral stenosis, with ipsilateral stenosis of 70% - 99% and contralateral stenosis of 50% - 69%) with a high ICA PSV showed a marked asymmetry of about -72 cm/s, with higher ipsilateral MCA velocity. Three cases with ICA stenosis in the range of 50% - 69% stenosis have asymmetries between 30 - 45 cm/s. We did not notice a large increase in velocity difference for the two patients with low ICA PSV. No correlation was observed between the MCA resistivity index (RI = 1– EDV/PSV) and ICA PSV, and RI was close to 0.6 for all subjects.

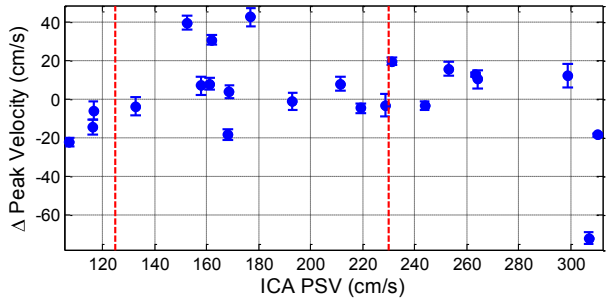

Figure 5. An error bar plot of the difference between peak systolic velocities (PSV) from middle cerebral arteries (MCA) contralateral and ipsilateral to an internal carotid artery (ICA) stenosis vs. the ipsilateral ICA PSV. The vertical red dashed lines are the ICA PSV cutoff points for 50% (left line) and 70% (right line) ICA stenosis.

V. Discussion

The clinical results tested the prediction of the simulations. In our sample population, we observed that the delays in the MCA waveforms seem to be independent of the severity of carotid stenosis. This confirms that the collateralization of the cerebral circulation influences hemodynamics downstream of carotid stenoses differently from other end organs. For example, in peripheral stenoses, the severity of stenosis is related to end organ pressure drop and a delayed flow waveform. This finding has implications for associating hemodynamic forces surrounding carotid stenoses with risk of plaque rupture. Hemodynamic forces may be one of the causes of intraplaque hemorrhaging, which is one of possible identifying factors of vulnerable plaque [2-5].

Both the manual and semi-automatic methods showed high cycle-to-cycle variability in the estimation of the delay between the ipsilateral and contralateral sides to stenosis. One possible cause of this variance is physiological variability. In our current study population, the delays in all cases were smaller than 50 ms. The semi-automatic method had larger delays, possibly because of noisy Doppler signals.

The simulation presented in this work was very simple, this was done so we can observe the effects that non-collateral cerebral flow has on MCA velocity waveforms. In the clinical data we were able to demonstrate the possibility of measuring delays from velocity waveforms of the MCA. We observed a trend towards an increase in MCA PSV asymmetry for higher ICA PSV, shown in Fig. 5. One case had a very high negative asymmetry, where positive asymmetries would be consistent with our simulations of non-collateral flow in the COW. A possible cause of the negative asymmetry was probably due to a distal ICA or an MCA stenosis on the ipsilateral side, causing higher MCA velocities. The increasing trend was not apparent in the pulse delays. This may be an indication of intracranial collateral flow for most of the patients studied in this work.

We were limited in this study due to the lack of concomitant imaging of the cerebral circulation to provide direct evidence of collateralization in the COW. Another limitation of our study is the small number of patients, which may not have included any cases with an incomplete COW based on the prevalence of incomplete COW. We are currently recruiting additional patients. Factors other than cerebral collateralization that may have been possible causes of delay or PSV asymmetries, include the insonation angle of the TCD transducer (only affects the PSV asymmetry and not the pulse delay); the anatomy, such as asymmetries in the COW vessel sizes, may cause delay and magnitude changes; and the downstream resistance of the microcirculation affected by vasodilation and vasoconstriction. The effect of these factors will be carefully examined in future studies.

VI. Conclusion

We have explored the possibility of using TCD to measure pulse delays in MCA velocity waveforms in the presence of carotid stenoses. Our simple linear model predicted that for an intact COW, there are no differences in flow, while for a disconnected COW, ipsilateral flow waveforms are delayed and of lower magnitude compared to the contralateral side. Even in the presence of severe ICA stenosis, we do not observe any significant bilateral asymmetries in MCA flow in all but one subject. A more detailed simulation of the neck and head circulation is needed to quantify the range of effects on the waveforms, which we are currently working on. More clinical data are needed to confirm our findings.

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