Hemodynamic differences in intracranial aneurysm blebs due to blood rheology

Marcelo A. Castro
CONICET. Universidad Tecnológica Nacional, Facultad Regional Buenos Aires
Grupo de Investigación y Desarrollo en Bioingeniería
Medrano 951, Ciudad Autónoma de Buenos Aires, CP 1179, Argentina
E-mail: marcelo.a.castro@gmail.com

María C. Ahumada Olivares
Universidad Favaloro, Facultad de Ingeniería, Ciencias Exactas y Naturales
Solís 453, Ciudad Autónoma de Buenos Aires, CP 1078, Argentina

Juan R. Cebral
George Mason University, College of Sciences
4400 University Drive, Fairfax, VA, 22030, USA

Abstract. Computational blood flow simulations over patient-specific image-based three dimensional domains under personalized flow conditions have been extensively used to investigate associations between flow characteristics and aneurysm initiation, progress and rupture. Although it is widely accepted that the wall shear stress is associated to those processes, there is still no agreement about what stress characteristics are responsible for triggering those biomechanical processes. Although the incorporation of the blood rheology in large arterial systems containing aneurysms resulted in similar hemodynamic characterizations for most aneurysms, large aneurysms, especially those containing blebs, are expected to have flow rates in the range where Newtonian and non-Newtonian models largely differ. However, there is no consent among authors about the impact of blood rheology on the intraaneurysmal wall shear stress magnitude. In this work we used high resolution models reconstructed from rotational angiography images to perform unsteady finite element blood flow simulations to investigate the differences in wall shear stress magnitude and alignment for Newtonian and non-Newtonian rheologies. Unstructured finite element meshes were generated using an advancing front technique. Personalized flow conditions were imposed at the inlets of the models. The Casson model was incorporated as a velocity-dependent apparent viscosity and the results were compared to those using the Newtonian rheology. Associations between the localization of regions with large differences in wall shear stress magnitude and orientation, and the regions of differentiated wall shear stress magnitude were studied in a cohort of patients.

1 To whom any correspondence should be addressed.
Introduction
During the last years some research groups have investigated the correlation between hemodynamic characteristic and initiation, development and rupture of cerebral aneurysms using numerical simulations. A previous study showed a possible association between high maximum WSS at the systolic peak and rupture in a cohort of AComA aneurysms [7]. A large study including 210 cerebral aneurysms at different locations it was found a statistical significant association between rupture and WSS distributions with elevated maximum WSS, high flow concentration and small impingement size [8]. Cebral et al. also showed a connection between location of aneurysm blebs and regions of high WSS in models where blebs were virtually removed [9]. In another study, it was presented a relationship between rupture, and coexistence of high WSS and high positive spatial WSS gradient, observed in three-patient scanned before and after aneurysm formation [10]. Although other investigators reported possible associations between low shear stress and either rupture [11,12] or blister formation [13], most experimental, clinical and numerical evidence suggest a connection between high WSS values and aneurysm formation. Particularly, the 20 vascular models harboring aneurysms in the middle cerebral artery reconstructed in [12], considered a limited portion of the parent artery, neglecting important features of the vascular geometry that resulted in a simplified simulated blood flow. Later, it was demonstrated that such simplifications significantly alter intra aneurysmal flow patterns [4].

Although most previous computational studies assumed that blood behaves as a Newtonian fluid, this assumption may not be completely accurate under some hemodynamic conditions. WSS in idealized models of saccular aneurysms was studied using Casson rheology under different flow conditions [14-16]. Particularly, Khanafer et al. showed that non-Newtonian wall shear stress is greater during the peak systole in aortic aneurysm models [15]. A limited number of patient-specific studies have been presented. Rayz et al. found no significant differences between low wall shear stress regions that may be associated with risk of thrombus formation using Newtonian and non-Newtonian computational fluid dynamic simulations in three patients [17]. However, accounting for non-Newtonian behavior improved the agreement with observations using longitudinal MRI studies. Xiang et al. showed that Newtonian viscosity model could overestimate normalized wall shear stress and consequently underestimate the risk of rupture of intracranial aneurysm in three internal carotid artery saccular aneurysms [18]. These results would suggest a dependence of WSS distributions on the real vascular geometry.

The purpose of this work is to compare the WSS values and orientation in patient-specific cerebral aneurysm models containing blebs where low flow is expected, using both Newtonian and Casson rheology in order to investigate regions of underestimation and overestimation of WSS in realistic geometries.

Materials and methods

1.1. Imaging and modeling
Five patients with cerebral aneurysms containing blebs were selected from our data base. Three dimensional rotational angiography (3DRA) images were acquired in four patients with aneurysms in the internal carotid artery (Cases #1, #2, #3 and #4) using a Philips Integris System (128³ voxels covering a field of view of 54.02 mm, with a voxel resolution of 0.422 mm), while the other patient with an aneurysm in the anterior communicating artery (Case #5) was imaged using dynamic computerized angiographic tomography at 19 time points along the cardiac cycle (512 x 512 x 205 pixels with a spatial resolution of 0.3125 x 0.3125 x 0.6125 mm covering a field of view of 16.0 x 16.0 x 12.81 cm.). Vascular modelling was performed using a previously presented methodology [3,7,19]. For the 4DCTA case, each three dimensional volume was cropped and averaged to reduce noise and computational cost. Masks were applied to differentiate internal carotid arteries from extravascular structures to properly reconstruct parent arteries, which is needed for a realistic blood
flow simulation. The vascular model was reconstructed from the average image. High-quality volumetric finite element grids composed of tetrahedral elements with an advancing front technique were generated for each case [20-22]. Element size was adjusted in order to approximately maintain the same number of elements in both large and small arteries, which resulted in grids containing up to 2.43 million tetrahedra (see Figure 1).

**Figure 1.** Vascular models for cases #1 (a, f), #2 (b, g), #3 (c, h), #4 (d, i) and #5 (e, j). First row corresponds to vascular models. Second and third rows correspond to unstructured grid of the computational domain from different views. Element size is adjusted to keep roughly the same number of elements across a cross-sectional area.

### 1.2. Numerical simulations

Finite element blood flow numerical simulations were performed using both Newtonian and non-Newtonian Casson rheologies. For the Newtonian case, blood was modelled as an incompressible fluid with attenuation 1.0 g/cm$^3$ and viscosity 0.04 Poise. For the Casson model, a velocity dependent apparent viscosity derived from that non-Newtonian model is computed at every mesh node (1)

$$\mu_{app} = \left( \frac{1}{\tau_0} - e^{-\frac{m\mu}{\dot{\gamma}}} \right)^2 + \mu$$

where $\tau_0$ is the yield stress, which was assumed as 0.09 gr (cm sec)$^{-1}$, $\mu$ is the Newtonian viscosity and $\dot{\gamma}$ is the shear strain rate. The exponent $m$, which is assumed greater than 10, is included in order for the apparent viscosity to be bounded for any range of shear strain rates [23].

The governing equations were the unsteady Navier-Stokes equations in 3D [24]. Vessel walls were assumed rigid, and no slip boundary conditions were applied at the walls. Pulsatile flow conditions derived from PCMR measurement in healthy subjects were imposed at the inlet of the models. Flow waveforms were scaled with the inlet area to achieve a mean WSS of 15 dyne/cm$^2$ at the inflow boundary of each model. This choice is consistent with studies relating vessel area and flow rates in internal carotid and vertebral arteries [25], as well as with the principle of minimal work expressed by Murray’s law [26]. Fully developed pulsatile velocity profiles were prescribed with use of the Womersley solution [1,27]. Assuming that all distal vascular beds have similar total resistance to flow, traction-free boundary conditions with the same pressure level were applied at outlet boundaries. The Navier-Stokes equations were numerically integrated by using a fully implicit finite-element formulation [3].
Maps of WSS magnitude were created to visualize the distribution of shear forces on the aneurysm wall for both Newtonian and Casson rheologies. The percent relative difference between both distributions was computed. Additionally, the angular difference of WSS vector orientations was also calculated. Above mentioned maps were compared in order to establish possible correlations and determine the impact of blood rheology on the underestimation or overestimation of WSS. Intraaneurysmal WSS was not normalized with respect to the parent artery values. Instead, normalization was achieved by scaling the mean flow rate inflow waveform using the cross-sectional area according to the principle of minimal work expressed by Murray’s law [26].

Results

Five vascular images exhibiting large aneurysms were selected from our data base. Cases #1 to #4 have aneurysms in the internal carotid artery. Particularly, cases #1 and #3 have the aneurysm in the bifurcation with the ophthalmic artery, while cases #2 and #4 are internal carotid siphon aneurysms. Cases #2 and #5 correspond to patients with a two-bleb aneurysm, while the other ones have multiple blebs on the aneurysm wall. The number of elements in the unstructured grids of tetrahedra depends on both the model size and the number of narrow vessels included in the model. Particularly, the AComA model (case #5) contains 2.43 million elements and 449 thousand points because it contains both left and right vasculature. However, ICA models reached up to 2.34 million elements and 4.25 thousand points because they include some small arteries where element size is automatically adjusted by means of sources that locally modify the element size from the background grid [28].

Cross sectional areas of the internal carotid arteries were used to scale the flow rates previously acquired using phase-contrast magnetic resonance imaging in a normal volunteer [29] in order to meet the criterion of minimal biological work for a typical mean WSS of 15 dyn/cm² at that artery [25].

For the wall shear stress analysis, distribution of the WSS magnitude at the systolic peak within the aneurysm wall was investigated for each case. Figures #2 through #6 correspond to cases #1 through #5. In all figures first and second row correspond to different views of the same aneurysm. First two columns show the maps of absolute value of WSS for both Newtonian rheology and Casson rheology, respectively. The relative difference between absolute values of WSS for Newtonian and Casson flows, is shown in the third column. Color maps range between blue (where the Newtonian WSS is as much as twice the Casson WSS) to magenta (where the Casson WSS is as much as twice the Newtonian WSS). Dark regions correspond to similar WSS values. Finally, the angle between the coplanar WSS vectors at each mesh node was computed and shown in the fourth column. Angles range from 0° to 20° for all cases but cases #4 where the angle ranges from 0° to 12°.

The first observation is that WSS distributions have similar characteristics for both rheologies. That result is in agreement with a previous sensitivity study [3]. The second observation is that large arteries, where greater flow rates are expected, have relatively larger WSS values for Casson model, which appears as dark red regions in the third column of Figures 2 through 6. This fact is in line with theoretical and computational results in simplified configurations and flow conditions [24,28]. The third observation is that not only WSS values differ between Newtonian and non-Newtonian rheologies, but also their vector orientation does. Those differences systematically take place in regions of low WSS. However, there is no clear correlation between regions with different WSS values, and regions where WSS vectors exhibit different orientations. In one of the blebs in case #1 large angular differences are associated to regions where any of the rheologies predict larger WSS values than the other one (compare Figure 3g to Figure 3h), however, that is not the case for case #4 (compare Figure 5c to Figure 5d, and Figure 5g to Figure 5h) where little WSS vectors have similar orientations despite their different magnitude values. Additionally, in the neck of one of the blebs of case #2, WSS vector orientations significantly differ in regions where WSS magnitude values do not.
Figure 2. Wall shear stress analysis for Case #1. First column (a, e): WSS maps for Newtonian rheology; Second column (b, f): WSS maps for Casson rheology; Third column (c, g): relative difference between the Newtonian and Casson WSS, where magenta indicates that Casson WSS is as much as twice the Newtonian WSS, blue indicates that Newtonian WSS is as much as twice the Casson WSS, and dark regions correspond to similar WSS values; Fourth column (d, h): difference in WSS vector orientation, where magenta represents a maximum of 20°.

Figure 3. Wall shear stress analysis for Case #2. First column (a, e): WSS maps for Newtonian rheology; Second column (b, f): WSS maps for Casson rheology; Third column (c, g): relative difference between the Newtonian and Casson WSS, where magenta indicates that Casson WSS is as much as twice the Newtonian WSS, blue indicates that Newtonian WSS is as much as twice the Casson WSS, and dark regions correspond to similar WSS values; Fourth column (d, h): difference in WSS vector orientation, where magenta represents a maximum of 20°.
Figure 4. Wall shear stress analysis for Case #3. First column (a, e): WSS maps for Newtonian rheology; Second column (b, f): WSS maps for Casson rheology; Third column (c, g): relative difference between the Newtonian and Casson WSS, where magenta indicates that Casson WSS is as much as twice the Newtonian WSS, blue indicates that Newtonian WSS is as much as twice the Casson WSS, and dark regions correspond to similar WSS values; Fourth column (d, h): difference in WSS vector orientation, where magenta represents a maximum of 20°.

Figure 5. Wall shear stress analysis for Case #4. First column (a, e): WSS maps for Newtonian rheology; Second column (b, f): WSS maps for Casson rheology; Third column (c, g): relative difference between the Newtonian and Casson WSS, where magenta indicates that Casson WSS is as much as twice the Newtonian WSS, blue indicates that Newtonian WSS is as much as twice the Casson WSS, and dark regions correspond to similar WSS values; Fourth column (d, h): difference in WSS vector orientation, where magenta represents a maximum of 12°.
Figure 6. Wall shear stress analysis for Case #5. First column (a, e): WSS maps for Newtonian rheology; Second column (b, f): WSS maps for Casson rheology; Third column (c, g): relative difference between the Newtonian and Casson WSS, where magenta indicates that Casson WSS is as much as twice the Newtonian WSS, blue indicates that Newtonian WSS is as much as twice the Casson WSS, and dark regions correspond to similar WSS values; Fourth column (d, h): difference in WSS vector orientation, where magenta represents a maximum of 20°.

Finally, for cases #1 through #4 there is no clear correlation either between low WSS regions and regions where any of the rheologies predict larger WSS values than the other one. Particularly, that is clearly observed in case #2 where Casson WSS is significantly greater or less than Newtonian WSS in regions of low WSS (compare Figure 3a to Figure 3c, and Figure 3e to Figure 3g). The same fact is also observed in case #4, when comparing Figure 5a to Figure 5c, and Figure 5e to Figure 5g. For case #5, Casson WSS is greater that Newtonian WSS in all arterial and aneurysmal wall. This difference is greater in regions of low shear stress, particularly, in the bleb that is not directly impacted by the inflow jet. On the other hand, in the impaction zone, which occurs in the other bleb, WSS values are roughly the same for both rheologies (see Figures 6 a-c and e-g).

Additionally, WSS was space-averaged over the parent artery (under relatively high WSS) and one of the blebs (under relatively low WSS), and the time evolution for case #2 and case #3 for both Casson and Newtonian rheologies was computed (see Figure 7). In arteries, Casson WSS is systematically higher than Newtonian WSS over the entire cardiac cycle (less than 10%), as shown in Figures 7a and 7c. However, for low WSS blebs findings differ. While in case #2 the same behaviour as in the artery is observed even for WSS values lower than 5 dyn/cm² (Figure 7b), for case #3 Casson WSS is higher than Newtonian WSS only around the systolic peak, where the WSS is higher. However, no threshold could be found, therefore for the same WSS value, Casson WSS may be higher than Newtonian WSS, or viceversa, depending on what part of the cardiac cycle is analysed.

Discussion
The purpose of this work is to investigate the differences between Newtonian and Casson WSS characteristics under a pulsatile flow condition at image-based aneurysm models. Our results corroborate that the smallest differences appear in high flow rate regions [24]. Besides, the WSS distributions do not exhibit significant differences among rheologies. This result is in line with a previous sensitivity study [3].

The characteristics of a non-Newtonian flow for idealized vascular models harboring aneurysms have been investigated in the past [14-16]. When a stationary flow in a rigid and straight pipe is
considered, WSS values are larger for a Casson flow than for a Newtonian rheology. This difference is more significant for low Reynold’s numbers [28]. However, when realistic geometries are considered under pulsatile regimes the differences must be investigated in a patient-specific basis. Rayz et al. found no significant differences between low wall shear stress regions that may be associated with risk of thrombus formation using Newtonian and non-Newtonian computational fluid dynamic simulations in three patients [17]. However, accounting for non-Newtonian behavior improved the agreement with observations using longitudinal MRI studies. Xiang et al. showed that Newtonian viscosity model could overestimate normalized wall shear stress and consequently underestimate the risk of rupture of intracranial aneurysm in three internal carotid artery saccular aneurysms [18]. These results would suggest a dependence of WSS distributions on the real vascular geometry. Fisher et al. studied a given number of rheologies in different idealized aneurysm models. It was found that spatially averaged Newtonian WSS was higher than the corresponding Casson WSS at the aneurysm dome during the whole cardiac cycle. The relative difference was higher during the diastole rather than the systole [16].

Figure 7. Space-averaged for case #2 (a and c) and case #3 (b and d), in the artery under a relatively high WSS (a and b) and a bleb (c and d). Casson WSS is plotted in blue, Newtonian WSS is plotted in red, and the difference between the Casson WSS and the Newtonian WSS is plotted in red.
The main finding is that there is no clear correlation between low WSS regions and regions where any of the rheologies predict larger WSS values. Particularly, large relative differences between Casson and Newtonian WSS may appear in a low WSS region (<10 dyn/cm$^2$). Additionally, flow in the internal carotid artery produces little greater WSS values for the non-Newtonian rheology with similar vector orientations. Finally, a non negligible change in WSS vector orientation is observed: as large as 20° in regions of low WSS. The location of those regions is not necessarily associated with regions where large differences in WSS occur when considering different rheologies. These observations may indicate that the realistic geometry plays an important role in the intra-aneurysmal hemodynamic characteristics, resulting in low flow regions where either the Newtonian or non-Newtonian WSS may be larger than the other one, exhibiting also differences in the vector orientation. However, considering that high WSS values are responsible for aneurysm initiation, growth and rupture, differences of WSS in regions of low WSS may not have a clinical impact [7,9,10,30]. Additionally, the rheology does not change the main hemodynamic characterization whose association with aneurysm initiation to rupture is investigated [28].

Given the small number of cases presented in this work, no statistical implications can be derived. However, these findings show some discrepancy with the results presented by Xiang et al. It is worth mentioning that the Casson model is only a possible representation that not necessarily depicts in an accurate manner the intensity and distribution of blood internal forces [16]. Finally, the same mean WSS was imposed at the inlets of the models based on the principle of minimal work expressed by Murray’s law [26]. Although that assumption is an approximation, it allows comparability when searching for associations between hemodynamic features and aneurysm risk factors [7,25,29]. Instead, Xiang et al. analyzed the WSS normalized with respect to the typical WSS values at the near parent artery [18], which may affect comparability.

Acknowledgements

Marcelo Castro wants to acknowledge CONICET (Consejo Nacional de Investigaciones Científicas y Técnicas) and MINCyT (Ministerio de Ciencia y Tecnología, PICT #279) for financial support.

References

[1] Taylor CA, Hughes TJR, Zarins CK, “Finite element modeling of blood flow in arteries. Computational Methods in Applied Mechanical Engineering 1998:158:155–196
[2] Steinman DA, Milner JS, Norley CJ, Lownie SP, Holdsworth DW. Image-based computational simulation of flow dynamics in a giant intracranial aneurysm. Am J Neurorad 2003:24(4):553-554
[3] Cebral JR, Castro MA, Appanaboyina S, Putman CM, Millán D, Frangi A. Efficient Pipeline for Image-Based Patient-Specific Analysis of Cerebral Aneurysms Hemodynamics: Technique and Sensitivity. IEEE - Transactions on Medical Imaging - Special Issue on Vascular Imaging 2005:24(4):457-467
[4] Castro MA, Putman CM, Cebral JR. Computational Fluid Dynamics Modeling of Intracranial Aneurysms: Effects of Parent Artery Segmentation on Intraaneurysmal Hemodynamics. Am J Neuroradiol 2006:27:1703-1709
[5] Nakatani H, Hashimoto N, Kang H, Yamazoe N, Kikuchi H, et al. Cerebral blood flow patterns at major vessel bifurcations and aneurysms in rats. J Neurosurg 1991:74:258-262
[6] Crompton M. Mechanisms of growth and rupture in cerebral berry aneurysms. Br J Med 1996:1: 1138-1142
[7] Castro MA, Putman CM, Cebral JR. Hemodynamic Patterns of Anterior Communicating Artery Aneurysms: A Possible Association with Rupture. Am J Neuroradiol 2009:30(2):297-302
[8] Cebral JR, Mut F, Weir J, Putman CM. Quantitative characterization of hemodynamic environment in ruptured and unruptured brain aneurysms. Am J Neuroradiol 2011:32:145-151
[9] Cebral JR, Sheridan M, Putman CM. Hemodynamics and Bleb Formation in Intracranial Aneurysms. Am J Neuroradiol 2010: 31:304-310
[10] Kulcsar Z, Úgron A, Marosfo M, Berentei Z, Paal G, Szikora I. Hemodynamics of Cerebral Aneurysm Initiation: The Role of Wall Shear Stress and Spatial Wall Shear Stress Gradient. Am J Neuroradiol 2011: 32(3):587-594
[11] Jou LD, Lee DH, Morsi H, Mawad ME. Wall Shear Stress on Ruptured and Unruptured Intracranial Aneurysms at the Internal Carotid Artery. Am J Neuroradiol 2008:29:1761-1767
[12] Shojima M, et al. Magnitude and role of wall shear stress on cerebral aneurysm: Computational fluid dynamic study of 20 middle cerebral aneurysms. Stroke 2004:35:2500-2505
[13] Shojima M, Nemoto S, Morita A, Oshima M, Watanabe E, Saito N. Role of Shear Stress in the Blister Formation of Cerebral Aneurysms. Neurosurg 2010:67(5):1268-1275
[14] Low M, Perktold K, Raunig R. Hemodynamics in rigid and distensible saccular aneurysms: A numerical study of pulsatile flow characteristics. Biorheol 1993:30:287-298
[15] Khanfer KM, Gadhoke P, Berguer R, Bull JL. Modeling pulsatile flow in aortic aneurysms: Effect on non-Newtonian properties of blood. Biorheol 2006:43:661-679
[16] Fisher C, Stroud Rossmann J. Effects of non-Newtonian behavior on hemodynamics of cerebral aneurysms. J Biomech Eng 2009:31:1-9
[17] Rayz VL, Boussel L, Lawton MT, Acevedo-Bolton G, Ge L, Young WL, Higashida RT, Saloner D. Numerical modeling of the flow in intracranial aneurysms: Prediction of regions prone to thrombus formation. Ann Biomed Eng 2011:36:1793-1804
[18] Xiang J, Tremmel M, Kolega J, Levy E, Natarajan S, Meng H. Newtonian viscosity model could overestimate wall shear stress in intracranial aneurysm domes and underestimated rupture risk. J Neurointerv Surg 2011:4(5):351-357
[19] Yim P, Vasbinder GB, Ho VB, Choyke PL. Isosurfaces as deformable models for magnetic resonance angiography. IEEE – Trans Med Imag 2003: 22(7):875-881
[20] Löhrner R. Extensions and improvements of the advancing front grid generation technique. Comput Meth Appl Mech Eng 1996:5:119–132
[21] Löhrner R. Regridding surface triangulations. J Comput Phys 1996:126:1–10
[22] Löhrner R. Automatic unstructured grid generators. Finite Elem Analysis Design 1997:25:111–134
[23] Pham TV, Mitsoulis E. Entry and exit flows of Casson fluids. Canad J Biomech Eng 1994:72: 1080-1084
[24] Mazumdar JN. Biofluid Mechanics 1992. World Scientific. Singapore
[25] Cebral JR, Castro MA, Putman CM, Alperin N. Flow-area relationship in internal carotid and vertebral arteries. Physiol Meas 2008:29(10):585-594
[26] Sherman TF. On connecting large vessels to small. The meaning of Murray’s law. J Gen Physiol 1981:78:431–453
[27] Womersley JR. Method for the calculation of velocity, rate of flow and viscous drag in arteries when the pressure gradient is known. J Physiol 1995:127:553–563
[28] Castro MA, Putman CM, Cebral JR. Computational Hemodynamics of cerebral aneurysms: Assessing the risk of rupture from hemodynamic patterns. VDM Verlag 2008. ISBN 9783639094411
[29] Cebral JR, Castro MA, Soto O, Löhner R, Alperin N. Blood flow models of the circle of Willis from magnetic resonance data. J Eng Math 2003:47(3/4):369-386
[30] Cebral JR, Mut F, Weir J, Putman CM. Association of hemodynamic characteristics and cerebral aneurysm rupture. Am J Neuroradiol 2011:32:264-270