# Hemodynamic Therapy of Middle Cerebral Artery Vasospasm Guided by a Multiphase Model of Oxygen Transport)

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**Abstract:** Cerebral vasospasm is a complication of subarachnoid hemorrhage and other neurosurgical emergencies that reduces blood flow to the brain. Part of the approach to management of vasospasm is to improve flow through the stenotic areas. A common practice is to reduce the hematocrit of the blood to decrease its viscosity and enhance flow through the stenosis. However, this reduces oxygen carrying capacity and potentially brain oxygen delivery. Since viscosity is a non-trivial inverse function of hematocrit, and oxygen content is directly related to hematocrit, actual oxygen delivery in critical stenosis is not easily predicted. To examine the interaction of these factors, we applied computational fluid dynamics coupled with oxygen transport at varying degrees of vasospasm of the first (M1) segment of the middle cerebral artery (MCA). Our goal was to determine the optimal hematocrit for oxygen transport for varying degrees of vasospasm. Single and two phase models were constructed of the MCA M1 geometry, and the models were solved at levels of stenosis ranging from 50% to 95%, and hematocrit values 0.2 to 0.6 (encompassing the normal and therapeutic values of .45 and .30). Our results indicate that at moderately severe stenosis, hemodilution reduces oxygen delivery through the stenotic segment. At extremely severe stenosis, improvement is seen at mild hemodilution, but the overall blood flow is so far below critical values that hemodilution would have to clinical benefit. This model does not address whether hemodilution has downstream effects which could be beneficial.

**Keywords:** Arterial stenosis, vasospasm, middle cerebral artery, hematocrit, oxygen delivery.

## 1. Introduction

Vasospasm in any of the three proximal intracranial arteries is a devastating sequelae of subarachnoid hemorrhage. The largest of these is the middle cerebral artery (MCA) which supplies much of the cerebral hemisphere. Treatment is both targeted and supportive. Targeted treatment consists of attempts to reduce the degree of stenosis by approaches such as angioplasty. Many patients are not candidates for targeted therapy, and supportive therapy is the only option.

One aspect of supportive therapy seeks to maximize blood flow through the stenotic area by reduction of the viscosity of blood to enhance its flow characteristics. Since viscosity is related to hematocrit, dilution of the blood volume to reduce its hematocrit (hemodilution) is frequently practiced. The drawback of hemodilution is that the oxygen carrying capacity of the blood is reduced. It remains unclear if the beneficial effects on viscosity and resultant improvement in flow outweigh the decrease in oxygen carrying capacity. i.e. does hemodilution actually improve oxygen delivery?

To address this question from a simulation perspective, a finite element model of the proximal segment of the middle cerebral artery was developed. This segment (M1 segment) is the initial segment from the origin of the artery to its first major branches and lies at the base of the brain. Vasospasm involving this artery can induce ischemia over a large portion of the cerebral hemisphere. Variable degrees of stenosis were introduced into the geometry, and for each level of stenosis, the hematocrit was varied from 0.2 to 0.6, representing the full range of values likely to be seen clinically. Of note, normal hematocrit is approximately 0.45, and therapeutic hemodilution targets a hematocrit of 0.30.

## 2. Methods

We evaluated two approaches. In the first, a single phase model of blood was used. Single phase models have long been used in blood flow simulation, and have demonstrated to represent blood rheology well at non-negligible shear rates and when blood vessel diameter is large in relation to RBC size (thus not accounting for the Fahraeus-Lindquist effect). The non-Newtonian nature of blood was modeled through empirical equations for viscosity as a function of hematocrit.

In the second approach we used a two-phase model of blood consisting of plasma and erythrocytes. Other cellular elements were disregarded. Two phase models have been increasingly adopted over the past several years, perhaps as computational methods and platforms have advanced. In this approach, overall mixture viscosity is not empirically defined but rather is determined by model conditions.

The primary purpose of including a single phase model was to provide a computational verification of the results of the two-phase model, but also to allow a comparison of these two approaches with alterations in vessel geometry.

### 2.1 Geometry model

The M1 segment is an arterial segment with an average diameter of 2.78 mm and a length approximately 11 mm long [1]. It branches off the distal internal carotid artery, then angulates sharply at the base of the brain before assuming a straighter course [2]. Vasospasm can involve a variable length of the MCA, including multiple segments. In this model, we limited the length of vasospasm to 80% of the length of the M1 segment.

The geometry was created in SolidWorks Office Professional 2008 (SolidWorks Corp., Concord, MA 01742, USA). A chord of length 11.9 mm was constructed that was representative of the path of the M1 segment. Ten subsegments were then created at evenly spaced distances and parameterized to create a consistent stenosis ranging from 0 (no stenosis) to .95 (95% diameter reduction). The segment was extended on each end by 2.5 mm to create straight entry and exit regions. An example of a geometry with a 70% stenosis is given in Figure 1.

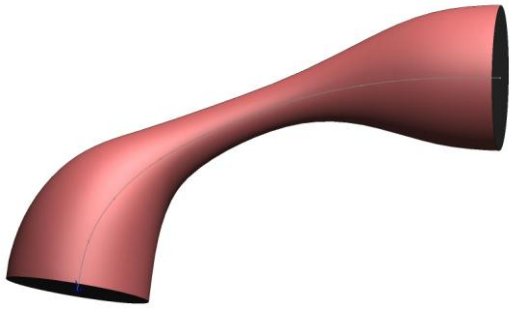

**Figure 1**. M1 segment geometry with 70% stenosis. The carotid inflow is at the lower left, and outflow at the upper right. The entry and exit regions are not shown in this figure.

Several geometries were constructed, ranging from 0 to 0.90 stenosis at intervals of 0.1, as well as levels of 0.95, 0.975 and 0.99. The geometry was imported into COMSOL Multiphysics v3.4 (COMSOL, Inc., Burlington, MA 01803, USA) using the SolidWorks Connection of the CAD Import Module. An unstructured mesh consisting of approximately 100,000 to 150,000 elements was generated for each.

### 2.2 Numerical Equations

Viscosity for the single phase model was estimated using an extension of the Carreau-Yasuda viscosity model [3,4], where *hct* represents the hematocrit:

$$\eta = m\left[1+\ \lambda\dot{\gamma}^{\ 2}\right]^{\frac{n-1}{2}}$$

$$m = 122.28\cdot hct^3 - 51.213\cdot hct^2 + 16.30\cdot hct + 1$$

$$n = .8092\cdot hct^3 - .8246\cdot hct^2 - .3503\cdot hct + 1$$

This formulation was also used for the mixture viscosity in the two phase model, since the Krieger and volume-averaged equations that provided in COMSOL do not appropriately reflect the non-Newtonian behavior of blood.

Oxygen transport was calculated according to the product:

$$D_{O_2} = \dot{Q}\cdot C_{O_2}$$

where $\dot{Q}$ represents blood flow and $C_{O_2}$ oxygen content of blood at the outlet. Diffusion of oxygen in plasma was assumed to be negligible.

### 2.3 Governing Equations

The single phase model was based on the stationary formulation of the Navier-Stokes equations with no external forces:

$$\rho\mathbf{u}\cdot\nabla\left[-p\mathbf{I}+\eta\ \nabla\mathbf{u}+\ \nabla\mathbf{u}^{\ \mathrm{T}}\right]$$

For two-phase flow, the mixture model formulation based on the Euler-Euler model for liquid droplets in a liquid continuous phase was used:

$$\rho\ \mathbf{u}\cdot\nabla\ \mathbf{u}=\nabla p-\nabla\ \rho\phi_d\rho_d/\rho\ 1-\phi_d\rho_d/\rho\ \mathbf{u}_{slip}\mathbf{u}_{slip}$$
$$+\nabla\ \eta\left[\nabla\mathbf{u}+\nabla\mathbf{u}^{\mathrm{T}}\right]$$
$$\rho_c-\rho_d\ \left[\nabla\ \phi_d\ 1-\phi_d\rho_d/\rho\ \mathbf{u}_{slip}\ +m_{dc}/\rho_d\right]+\rho_c\ \mathbf{u}\cdot\nabla$$
$$\nabla\left[\phi_d\mathbf{u}+\phi_d\ 1-\phi_d\rho_d/\rho\ \mathbf{u}_{slip}\right]=m_{dc}/\rho_d$$

The Schiller-Naumann model was chosen for the slip velocity, and has been used by other investigators for blood flow simulation [1]. The mixture viscosity model chosen was the same as for the single phase model (see Section 2.2 above).

### 2.3 Boundary Conditions

Three boundary conditions were defined. The inlet condition was a pressure held constant at 100 Pa. This value yielded flows that approximated reported values with no stenosis present. The outlet was a pressure held constant at 0 Pa. A no-slip condition was used for the walls of the arterial segment.

These conditions assume a constant downstream pressure drop. It is recognized that under changing physiological conditions that the downstream impedance will vary according to viscosity and oxygen content as well as the release of vascular mediators during ischemia. Since these conditions are highly unpredictable, the constant pressure drop chosen for this model likely represents a best-case scenario, but is recognized as a limitation of the model.

### 2.4 Model Solution and Postprocessing

The model was solved in stationary mode for the lower bound of hematocrit using the PARDISO solver in segregated solver mode. The three segregated group components were velocity and pressure variables, dispersed phase fraction (hematocrit), and slip velocity, respectively. The parametric solver component was then included to solve for hematocrit ranging from 0.2 to 0.6 in steps of 0.05.

Oxygen transport was then calculated using the product of outlet velocity and oxygen content calculated based on hematocrit (dispersed phase fraction), assuming a relationship of 33 grams of hemoglobin per deciliter per unit hematocrit.

## 3. Experimental Results

### 3.1 Velocity profiles

The velocity profiles of the single and two phase studies were nearly identical for all degrees of stenosis. Solutions for the 70% stenosis at a hematocrit value of 0.2 (low viscosity) are given for the single and two phase model in Figures 2 and 3, respectively:

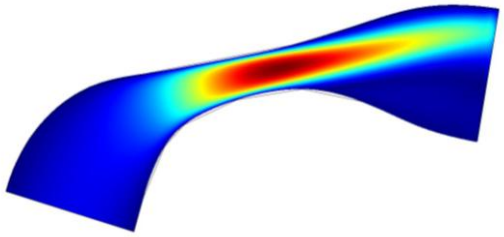

**Figure 2**. Longitudinal section plot of single phase mixture velocity at 70% stenosis and hematocrit 0.20. Peak velocity value was 0.43 m/s.

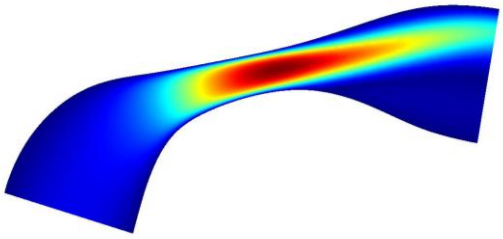

**Figure 3**. Longitudinal section plot of two phase mixture velocity at 70% stenosis and hematocrit 0.20. Peak velocity value was 0.42 m/s.

Solutions for the 70% stenosis at a hematocrit value of 0.6 (high viscosity) are given for the single and two phase models in Figures 4 and 5, respectively:

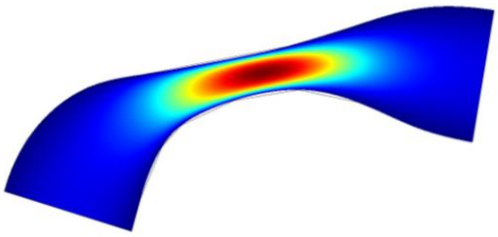

**Figure 4**. Longitudinal section plot of single phase mixture velocity at 70% stenosis and hematocrit 0.60. Peak velocity value was 0.25 m/s.

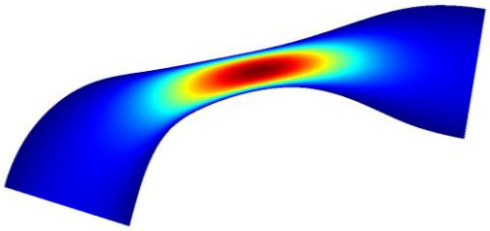

**Figure 5**. Longitudinal section plot of two phase mixture velocity at 70% stenosis and hematocrit 0.60. Peak velocity value was 0.24 m/s.

### 3.2 Blood flow

Blood flow through the stenotic segment was determined by integration of outlet velocity. There were slight differences between the single and two phase models. These differences were noted for both the degree of stenosis and the hematocrit. This behavior is demonstrated in Figures 6 and 7 for two levels of stenosis:

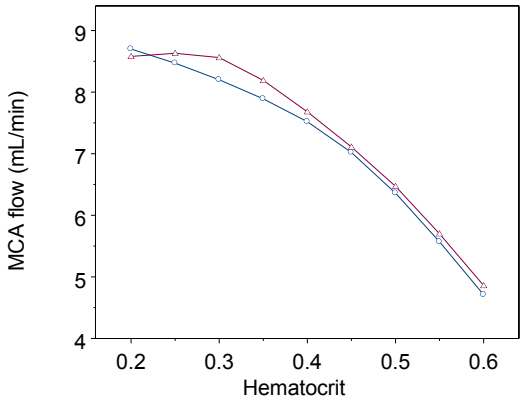


**Figure 6**. Plot of blood flow for the single (circles) and two phase (triangles) models at a stenosis level of 0.7. The data are shown for each level of hematocrit.

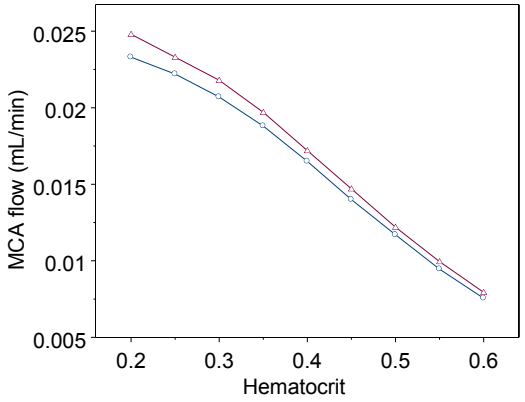


**Figure 7**. Plot of blood flow for the single (circles) and two phase (triangles) models at a stenosis level of 0.95. The data are shown for each level of hematocrit.

### 3.3 Oxygen delivery

Oxygen delivery through the stenotic segment was determined by the product of hematocrit and the velocity integrated over the outlet boundary. For the two phase model, the hematocrit varied over the outlet boundary, so it was determined by integrating the product of local hematocrit and velocity. The dependence of oxygen delivery on hematocrit at two levels of stenosis is shown in Figures 8 and 9.

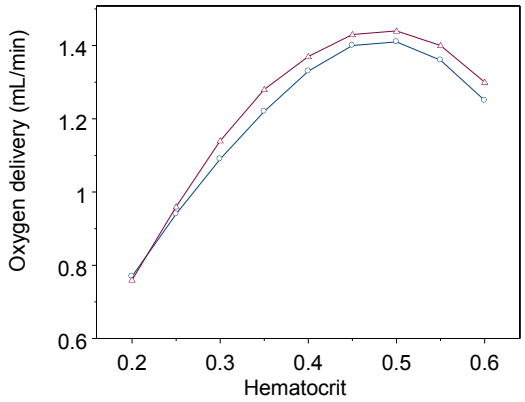


**Figure 8**. Plot of oxygen delivery for the single (circles) and two phase (triangles) models at a stenosis level of 0.7. The data are shown for each level of hematocrit.

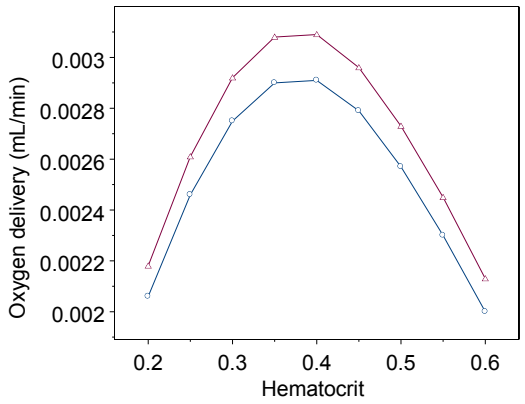


**Figure 9**. Plot of oxygen delivery for the single (circles) and two phase (triangles) models at a stenosis level of 0.95. The data are shown for each level of hematocrit.

There is a trend for oxygen delivery to improve with decreasing hematocrit. At moderately severe stenosis (70%), however, the maximum delivery occurs at a hematocrit above normal (.45). With extremely severe stenosis (95%), there is a trend toward improved oxygen delivery with hemodilution. However, maximal delivery is still above the target hematocrit, and most importantly, the overall oxygen delivery at such severe levels of stenosis is so far below critical values that hemodilution would have no clinical impact.

## 4. Discussion

Clinical practice for the management of cerebral vasospasm has long been guided by the assumption that hemodilution and its attendant reduction in viscosity could improve blood flow to ischemic brain. The assumption has been that this improvement outweighed any reduction in oxygen carrying capacity. The results of this model, however, suggest otherwise, in that oxygen delivery drops with hemodilution except in the most severely stenotic lesions. In the latter, however, overall blood flow is so far below critical values that alteration of hematocrit is not likely to have any clinical impact.

Recent clinical trials that have evaluated outcome following hemodilution suggest that this therapy does not diminish neurologic injury, but have not addressed the fundamental mechanisms in terms of the determinants of oxygen delivery. This project demonstrates that the balance between viscosity and oxygen carrying capacity indicates that oxygen delivery through the stenotic segment is not improved by hemodilution.

There are several limitations of this model. Most importantly we did not include downstream resistance, which could produce a different pressure drop across the stenosis than the fixed pressure drop of 100 Pa used in this model. The downstream resistance is not predictable since it is influenced by numerous factors, and our model could not include it. In particular, hemodilution could conceivably result in a lowering of downstream resistance, which would improve perfusion by increasing the pressure gradient across the stenosis.

## 5. Conclusions

This simulation project provides evidence that hemodilution used as part of the management of vasospasm of the intracranial arteries, such as that following subarachnoid hemorrhage, does not improve oxygen delivery across the stenotic segment. To the contrary, the results demonstrated herein suggest that ischemia could be worsened with the application of hemodilution, unless hemodilution resulted in a reduction in downstream resistance that would increase the trans-stenotic gradient and improve blood flow

## 6. References

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## 7. Acknowledgements

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