

# **Induced Disturbed Flow Through Vasoconstriction of Blood Vessels Supplying Cancerous Tumors**

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## **Abstract**

Cancerous tumors require a source of oxygen and nutrients to survive— just like every other cell in the body. Unlike other cells in the body, however, cancerous tumors differ from the normal physiological actions and anatomical structure of the body. As a result, they require a mode to receive the necessary oxygen and nutrients to survive. In order to accomplish this, cancerous tumors undergo a process called angiogenesis, or the recruitment of new vessels. This angiogenesis creates a complex network of tumor vasculature that supplies the tumor with the required amount of oxygen and nutrients to survive and grow. Blood flow to the tumor is an important physiological process to investigate in order to discover proper treatment methods to stall or kill cancer development. This study will investigate the fluid dynamics of two separate versions of the same tumor vasculature. We will have a model of tumor vasculature (our control) and an additional model with vasoconstriction. Essentially, we are analyzing the effects of vasoconstriction (oftentimes referred to as tumor vasculature disruption) of the afferent end of tumor vasculature on blood flow dynamics. We will perform both ANSYS simulation and a visualization with a 3D printed model and dye within a flow tank. We believe that under vasoconstricted conditions blood flow will decrease to the tumor which, in theory, would restrict the supply of nutrients and oxygen. Additionally, outlet velocity would decrease in the vasoconstricted vasculature as well as an increase in pressure at the site of vasoconstriction. Also, pressure should increase at the inlet and at the site of vasoconstriction. Our results suggest that outlet velocity did decrease significantly in the constricted case. Additionally, pressure increased in the inlet of the vasoconstricted case as well as at the site of vasoconstriction. Wall shear stress was visualized between the control and the constricted case and wall shear was found to increase especially at and around the site of vasoconstriction.

## **Introduction**

Cancerous tumor “...growth in the vascular network is important since the proliferation, as well as metastatic spread, of cancer cells depends on an adequate supply of oxygen and nutrients and the removal of waste products.” (Nishida, 2006). This process is called angiogenesis, or the recruitment of new vessels. This angiogenesis creates a complex network of tumor vasculature that supplies the tumor with the required amount of oxygen and nutrients to survive and grow. Anti-angiogenesis techniques are a common source of cancer research as a “...number of anti-angiogenesis drugs have been FDA-approved and are being used in cancer treatment, and a number of other agents are in different stages of clinical development or in preclinical evaluation.” (Rajabi & Mousa, 2017). Blood flow to the tumor is an important physiological process to investigate in order to discover proper treatment methods to stall or kill cancer development. Investigation of fluid flow has been done in tumor vasculature but at low-velocities and using a novel technique called, convection-MRI (Walker-Samuel et al., 2018). This study’s focal point was on the technique of convection-MRI and how it can be a novel technique in measuring low-velocity fluid flow in tumors among other components. However, our analysis will investigate the effect of vasoconstriction on the fluid dynamics of tumor

vasculature, a feature that was not investigated within this study. Other work has also been done involving tumor vasculature and the influence of “Tumor-Vascular Disrupting Agents” on different treatments of cancer (Siemann, 2012). This study however, lacks mathematical data regarding fluid dynamics. CFD simulation has been done “to analyze the effect of blood flow dynamics” in hepatic based tumors (Taebi et al., 2021). These are done for specific cases however they don’t explore the simulation after treatment which restricts angiogenesis.

In this study, we will investigate the effects of vasoconstriction on the fluid dynamics of blood through tumor vasculature. To accomplish this, we will use two models derived from the same vasculature in order to compare blood flow with and without vasoconstriction. One model will have an induced vasoconstriction at the afferent site of the vessel (Figure 3) while another will not (Figure 2). We will also analyze flow of the vasculature within a flow tank using fluorescent dye. We believe that under induced disturbed flow (vasoconstriction), exit velocity of blood will decrease dramatically within the tumor. Additionally, we hypothesize that pressure will drastically increase at the site of vasoconstriction and shear wall stress will also increase at and around the site of vasoconstriction. We confirmed these hypotheses through ANSYS simulation in which we tested pressure, velocity, and wall shear stress.

The results were as expected; exit velocity decreased while pressure and shear wall stress increased around the site of vasoconstriction. Another aspect of the analysis was velocity curl. We saw an abrupt increase in velocity curl around the site of vasoconstriction compared to the control. These results verify that vasoconstriction severely decreases blood flow and therefore would limit oxygen, nutrient, and waste flow to and away from a tumor.

## Methods

### Model Creation

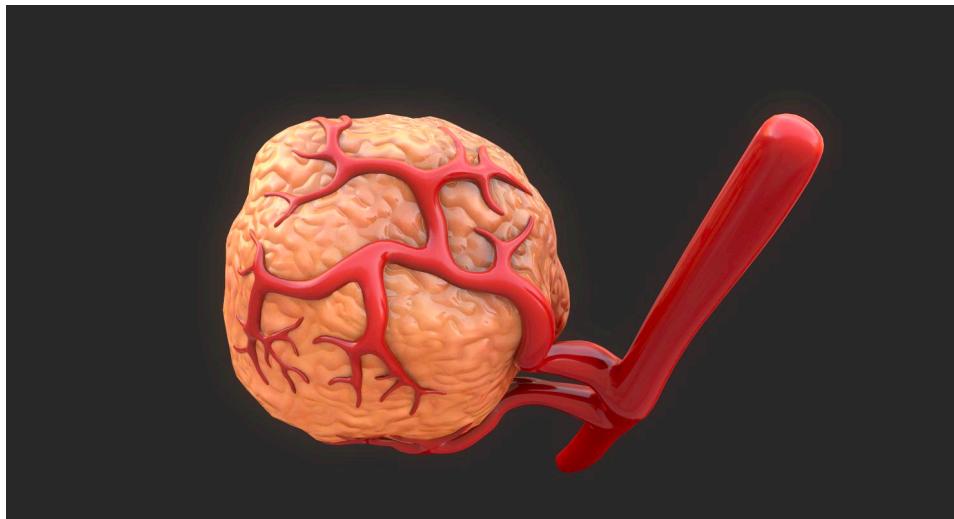
Tumor vasculature is a difficult model to replicate as it is highly based on hypotheticals. The location of a tumor can greatly impact the ability for angiogenesis to occur and from which vessel it may originate from. With this in mind, the model that I’ve chosen to use is not completely anatomically accurate in terms of diameter, length, and overall structure of the vasculature. However, with that in mind, no two tumors have the same vasculature therefore, the following simulation and analysis will differ between different cancers and tumors with different vasculature. Luckily, the analysis we are conducting is a general analysis that will give insight into the effects of vasoconstriction on blood supply to a hypothetical tumor.

The model used in our analysis is an adaptation of a model found on “<https://free3d.com/>”. The existing model was manipulated using the software, Meshmixer, to remove the tumor mass while leaving the vasculature intact. This was done by isolating the two layers from each other and removing the tumor layer. This process could have also been done in any CAD software but since other features from Meshmixer were also used, I decided to remain within that software. Within the original model, a large blood vessel (the site of the origin of the angiogenesis) was present. This blood vessel was removed using AutoDesk Fusion 360. (NOTE: for professors, since I wasn’t the one who actually manipulated the model this way, should I mention that it was done for me or explain how I would’ve done it?) Additionally, the model

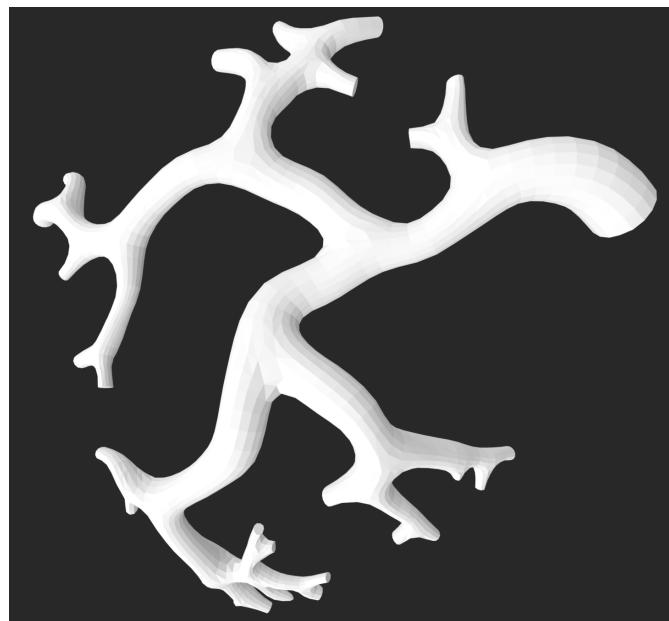
needed further manipulations in order to prevent complications with the ANSYS simulation. Consequently, the inlets and outlets (distal ends of vasculature) were smoothed to resemble a face of a cylinder. This simplification, while not anatomically accurate, will ensure the ANSYS simulation can perform our analysis properly. Figure 1 below displays the original model while Figure 2 represents the aforementioned changes.

An additional model was created to support our actual analysis and answer our essential question for this paper: how will vasoconstriction of the inlet of tumor vasculature affect blood flow to the tumor? This 3rd model is a further modification of the already modified model shown in Figure 2. To create this model, the brush feature in Meshmixer was used to replicate vasoconstriction in the afferent vesicle at a point of interest near the inlet. This third model can be seen in Figure 3 below.

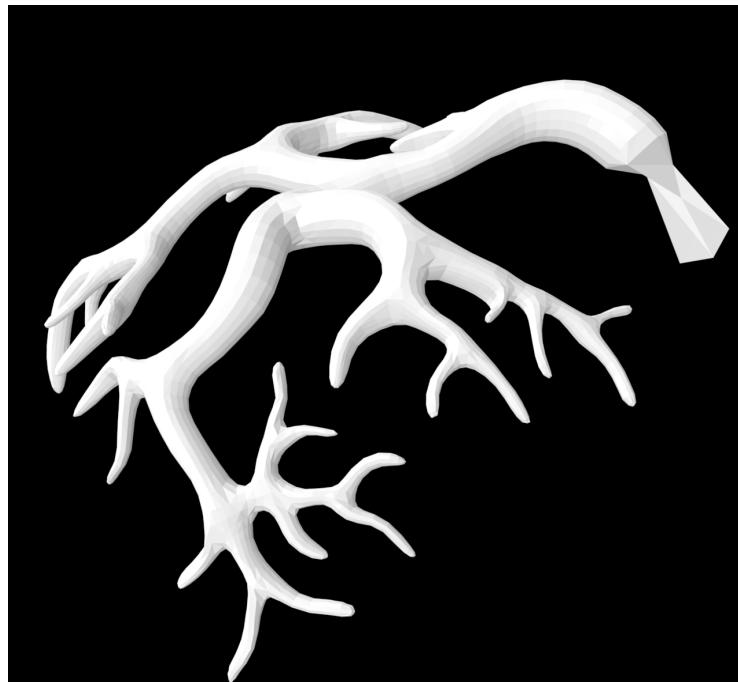
A fourth model was created using Meshmixer in which we took the inverse of the vasculature into a block and 3D printed it using PLA. Meshmixer was used to invert the model using the Boolean tool. This was exported as an .STL and loaded into PrusaSlicer. PrusaSlicer was used to position the block and slice for a .gcode. The model was printed on a commercial 3D printer. This model was used to analyze flow using a fluid flow tank and fluorescent dye. Figure 4 shows this model.



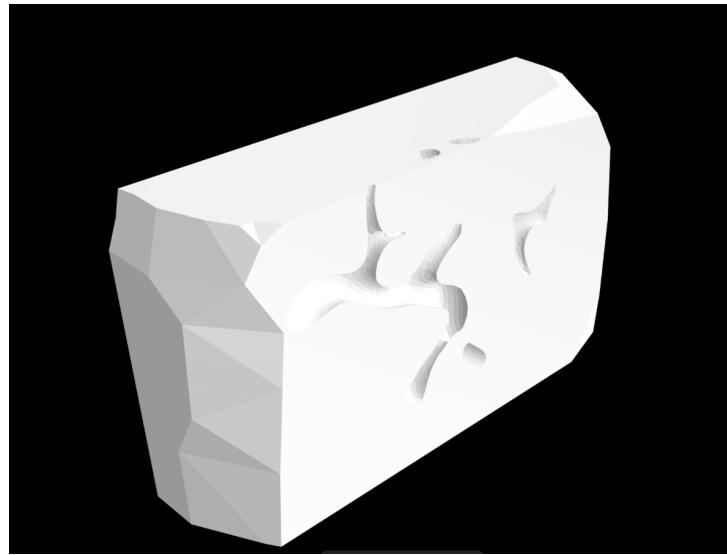
**Figure 1:** Original Model from free3d.com with large vesicle, tumor and vasculature shown.



**Figure 2:** Modified Model with large vesicle, tumor, and portions of vasculature removed. Additionally, vasculature inlets and outlets are smoothed and flattened.



**Figure 3:** Modified Model with Vasoconstriction applied. Large vesicle, tumor, and portions of vasculature removed.



**Figure 4:** Inverted Model Mold for 3D printing and fluid flow analysis via flow tank and fluorescent dye.

### Pre-Experiment Computations

Before using the models and running simulations. First, background research was done to estimate the Reynolds' number of blood flow through cancer tumor vasculature. This way, we can assess whether the flow can be considered laminar or turbulent.

The Reynolds number ( $Re$ ) is given as:

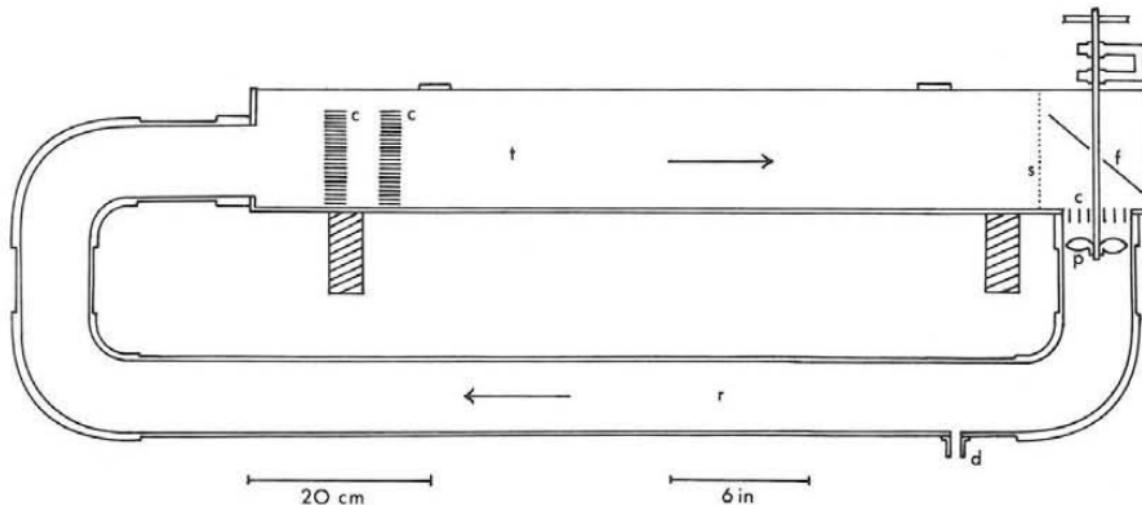
$$Re = \rho L U / \mu \quad (1)$$

In this context,  $U$  represents the characteristic or average velocity within the vasculature,  $L$  denotes the vessel diameter,  $\mu$  stands for the blood's dynamic viscosity, and  $\rho$  indicates blood's density. It is difficult to estimate the diameter of tumor capillaries because of the large discrepancy between each case. Based on previous works, “the mean diameter of capillaries in healthy and cancerous tissues corresponds to  $(8.0 \pm 1.1) \mu\text{m}$  and  $(3.9 \pm 1.1) \mu\text{m}$ , respectively.” (Lang et al., 2012). This work, however, is based on research on mice. Instead, while not entirely scientific, I will use the ratio between healthy and cancerous tissues from this paper to estimate the diameter of the cancerous capillaries in humans. Based on multiple sources, healthy human capillaries vary from  $8\text{-}10 \mu\text{m}$ . For the sake of assuming that healthy capillaries extracted from the same site as the mice (the colon) would be larger, we'll assume that healthy capillaries are  $10 \mu\text{m}$  in diameter. As a result, using the ratio of healthy to cancerous tissue capillaries from the study by Lang et al., we can make an educated inference of a cancerous tissue capillary diameter of  $10 \mu\text{m}$ . Blood flow velocity is also very difficult to predict due to disparity between each case of cancer vasculature. However, we will use the ranges found from a paper analyzing velocity in microcirculation for our blood flow velocities,  $0.1$  to  $2.2 \text{ mm/s}$  (Ye et al., 2020). For this example, we'll use  $1 \text{ mm/s}$  for characteristic velocity to simplify the calculation. The dynamic viscosity of blood is about  $3.5 \times 10^{-3} \text{ Pa}\cdot\text{s}$ , and the density is  $1050 \text{ kg/m}^3$ . The Reynolds' number is calculated to be about  $0.003$  which is in the laminar regime. A Reynolds number of approximately  $0.003$  is a reasonable estimation for flow in tumor

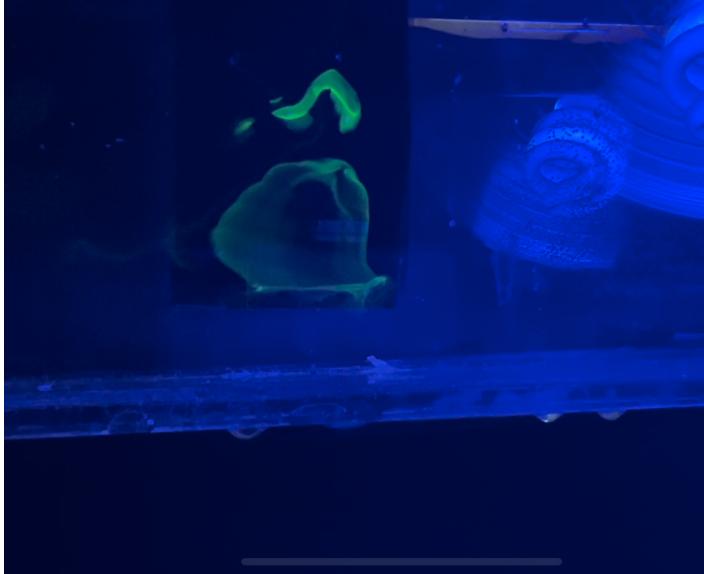
vasculature. This low value aligns with the characteristics of blood flow in very small vessels, which is typically in the laminar flow regime due to the small vessel diameters and low velocities. In tumor vasculature, blood flow often experiences additional resistance and irregularities due to vessel structure and abnormal morphology. Low Reynolds numbers suggest that the flow remains viscous-dominated and smooth, which is consistent with microcirculatory environments. We will use these estimations later as a basis for further understanding the fluid dynamics of the blood flow in cancer capillaries. Primarily, we will compare the velocity values from ANSYS to the estimated values we have estimated here from prior literature.

#### Flow Visualization with Fluorescent Dye in a Flow Tank:

The 3D-printed tumor vasculature (Figure 4) was placed in a desktop flow tank with a 4.5" x 5" cross section, filled with water to simulate the blood flow (see Figures 5 and 6). The desktop flow tank was designed after Vogel and LaBarbera (1978). To analyze the flow, the top side of the 3D printed tumor vasculature was placed flush to the front panel of the flow tank with a clamp. Then, fluorescein dye was inserted into the inlet using a standard fluid dropper. The flow was visualized and quantified using Fiji/ImageJ. A video was uploaded to ImageJ and using frame-by-frame analysis, flow velocity was estimated (~1.3 mm/s). Further analysis of the flow of vasoconstriction within the flow tank was not pursued. The reliability of the flow tank in quantifying velocity was not as efficient as other forms of simulation. Therefore, the creation of a second 3D model with vasoconstriction applied to the inlet was not performed. However, if this analysis was to be performed, another video taken with the same flow tank velocity would be recorded in which velocity would be estimated using the aforementioned ImageJ analysis.



**Figure 5:** Flow tank design used for physical visualization of flow through 3D printed tumor vasculature.



**Figure 6:** Visualization of fluid flow through inlet to outlets of tumor vascularization in the non-constricted case.

#### Computational Fluid Dynamic Analysis Using ANSYS & Navier-Stokes Equation

ANSYS Fluent (2022) was used to simulate flow of the model shown in Figure 2 and Figure 3. In this analysis, the wall shear, pressure, and velocity were all modeled and simulated for both the vasoconstricted case and the normal vasculature case. A relevant equation to these simulations is the Navier-Stokes Equation:

$$\rho(u \cdot \nabla)u = -\nabla p + \mu\Delta u + f, \quad (2)$$
$$\nabla \cdot u = 0$$

Here,  $\rho$  represents the blood density,  $u$  denotes the velocity field,  $p$  is the pressure field,  $f$  indicates external forces, and  $\mu$  is the dynamic viscosity of the blood.

The blood was modeled as a Newtonian fluid with a density of  $1055 \text{ kg/m}^3$  and a dynamic viscosity of  $3.5 \times 10^{-3} \text{ Pa}\cdot\text{s}$ . The inlet was defined as the largest aperture on the vasculature for both the vasoconstriction case and the normal case. From Figure 2 it is the aperture that is farthest to the right and the same for Figure 3. Outlets were defined as all other apertures in the models.

The simulation was run until convergence was achieved, indicating that a steady-state solution was found. Post-processing was conducted to analyze and visualize velocity streamline, velocity vectors, pressure contours, and wall shear for both cases. This data provides insight into the fluid dynamic changes caused by a vasoconstriction at the inlet of a tumor vasculature, crucial for supplying cancerous tumors with nutrients and oxygen.

## Results

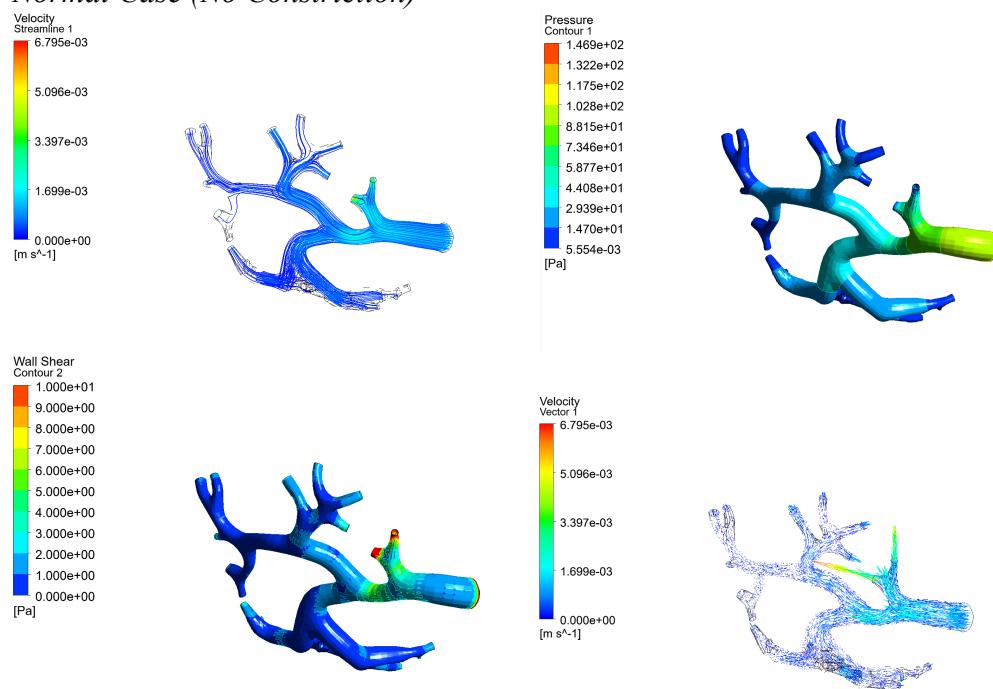
### Flow Tank Visualization:

Figure 6 shows the flow of the fluorescein dye through our 3D printed tumor vasculature (see figure 4). The maximum flow velocity was estimated at about 1.3 mm/s. This analysis was done through ImageJ. A .mp4 file video of the flow was imported into ImageJ at 60 fps in which the image was broken down frame-by-frame. The scale of the image was defined based on the dimensions of the 3D printed model. Manual tracking was performed using the Point Tool. The data was then exported and velocity was calculated by dividing the distance of the initial and final points by the time. This gave the value of ~1.3 mm/s. This value alone is not useful to the overall analysis however, further exploration using a second model with vasoconstriction could help understanding the effects of vasoconstriction on exit velocity.

### Numerical Simulations:

The following section will show results/images of the ANSYS simulation. The first subsection will show examples from a non-altered tumor vasculature (no constriction). The second subsection will show examples in which the appendage closest to the inlet is vasoconstricted.

#### *Normal Case (No Constriction)*

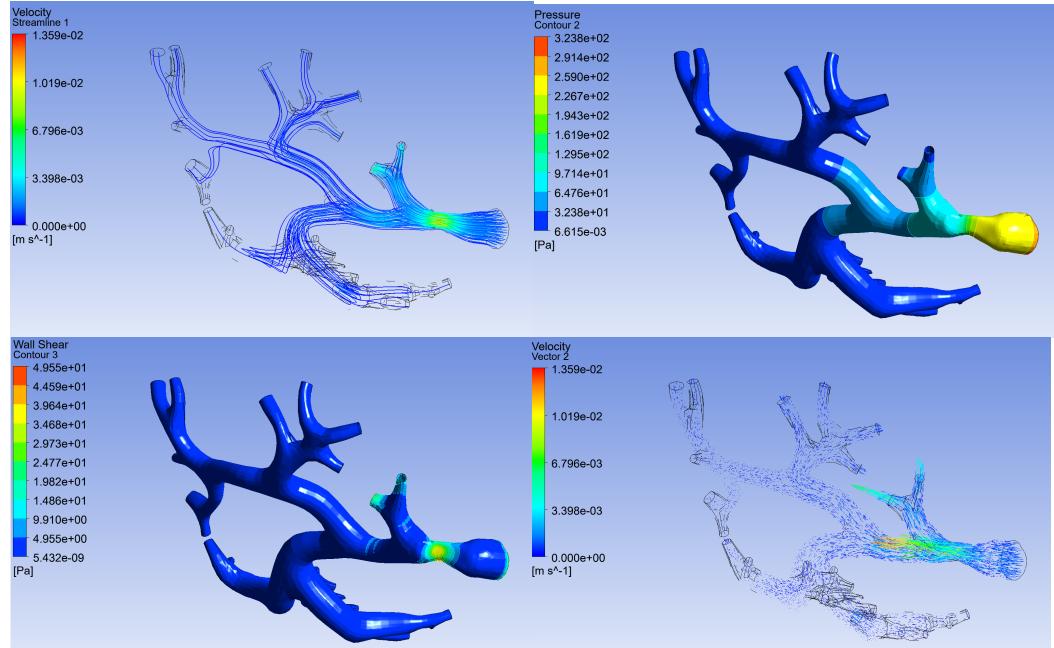


**Figure 7:** Results from ANSYS Simulation showing velocity streamline (top left), pressure contour (top right), wall shear contour (bottom left), & velocity vectors (bottom right).

Figure 7 shows the colormaps for the 3 different variables we are comparing between the normal and vasoconstricted case. For the sake of easier analysis I will discuss the important

comparison points in a later section. An interesting point to note is the increased wall shear at the first two outlets as well as the wall shear at the inlet.

### Vasoconstriction Case



**Figure 8:** Results of vasoconstriction from ANSYS Simulation showing velocity streamline (top left), pressure contour (top right), wall shear (bottom left), & velocity vectors (bottom right).

Figure 8 shows the results and colormaps of velocity, pressure, and wall shear. As expected, pressure was drastically increased at the inlet due to vasoconstriction.

### Comparison Between Both Cases

Comparing the two ANSYS simulations, one can see a clear change due to vasoconstriction which affects all three variables. For one, the colormap of wall shear shows an increase in wall shear at the site of vasoconstriction; this site had the highest value of wall shear (~39 Pa). Upon analysis, the wall shear of the inlet and first two outlets remained relatively constant between both the vasoconstriction case and normal case (~14.86 Pa). The scaling of velocity increased between the normal case and the vasoconstriction case. However, this does not necessarily indicate an increase in velocity within the vasculature due to vasoconstriction. While there was an increase in velocity near the high pressure points, velocity at the efferent ends of the vasculature actually decreased. Additionally, a look at the velocity vectors will show a decrease in the vector instances which is a good indicator of a decreased amount of flow in those areas. Therefore, less blood flow to the actual tumor would result from this. We know that pressure and velocity are directly related so an increase in velocity would indicate an increase in pressure at the site of vasoconstriction. According to Figure 8 (top left), there was an increase in pressure not only at the site of vasoconstriction but throughout all of the vasculature. This would align with physiological logic as, for example, those with clogged arteries will experience an overall higher blood pressure. Overall, these ANSYS results show the effects of vasoconstriction on blood flow to a tumor based on the comparison between the two cases described above.

## Discussion

The results of this study demonstrate the effect of vasoconstriction on blood flow dynamics in tumor vasculature, offering potential insights into approaches for limiting tumor growth and survival. Through both flow tank visualization and ANSYS simulations, we observed the influence of induced vasoconstriction on outlet velocity, pressure, wall shear stress, and velocity curl. Our findings indicate that vasoconstriction restricts blood flow to the tumor, a conclusion that aligns with our initial hypotheses and is supported by the observed decreases in outlet velocity and increases in both inlet pressure and wall shear stress near the site of constriction.

One of the most significant observations in this study is the sharp increase in pressure at the site of vasoconstriction, which extended throughout the vasculature in the vasoconstricted model. This rise in pressure is due to the constricted geometry at the inlet, which increases resistance to blood flow. Physiologically, this reflects conditions seen in cases of arterial narrowing, where restricted blood vessels lead to elevated upstream pressure. Within the context of tumor vasculature, this resistance not only restricts the tumor's access to nutrients and oxygen but may also increase mechanical stress in the tumor microenvironment. The heightened wall shear stress observed at and near the site of vasoconstriction supports this effect, as shear forces are known to impact endothelial cell behavior and may potentially compromise the structural integrity of tumor vessels.

Another notable result is the decreased velocity at the efferent ends of the vasculature in the vasoconstricted case. This reduction in flow could limit the tumor's access to essential nutrients and oxygen needed to sustain rapid growth. Tumor cells rely heavily on a consistent supply of resources to maintain accelerated proliferation rates, so any reduction in blood flow represents a plausible mechanism to impair tumor survival. By starving the tumor cells of necessary nutrients and oxygen, vasoconstriction may increase the tumor's vulnerability to anti-cancer therapies.

Additionally, the observed increase in velocity curl around the site of constriction provides further evidence of disrupted flow. This result indicates greater flow disturbance, likely due to turbulent-like behavior caused by abrupt changes in vessel geometry. While tumor blood vessels are already irregular and tortuous, further constriction appears to exacerbate these effects. Such disrupted flow could hinder efficient exchange processes within the tumor vasculature, contributing to hypoxic conditions. Although hypoxia can sometimes support tumor survival, it can also make tumors more susceptible to specific treatments targeting low-oxygen environments.

These findings are consistent with existing research on the use of CFD in modeling blood flow within tumor vasculature and exploring the mechanical impacts of treatments aimed at limiting angiogenesis. The data support the concept that targeting blood supply pathways through vasoconstriction could complement anti-angiogenesis drugs and potentially enhance their therapeutic effects. Moreover, ANSYS simulations provide a controlled way to adjust model parameters, opening possibilities for future studies to optimize these constriction effects or examine different flow rates and vascular structures across various tumor types.

However, limitations exist within this study. The model's simplifications—such as uniform vessel diameters and idealized vasculature—do not fully replicate the anatomical complexity of actual tumor blood vessels. Future research could incorporate more anatomically accurate tumor models and account for the non-Newtonian properties of blood to better reflect real biological conditions. Although the ANSYS simulations yielded valuable insights, further in vitro or in vivo studies would be necessary to validate the findings and assess the practical feasibility of vasoconstriction as a therapeutic approach.

In conclusion, this study contributes to the understanding of tumor vasculature mechanics by demonstrating the potential benefits of inducing vasoconstriction to limit blood flow to tumors. By reducing the delivery of nutrients and oxygen, increasing internal pressure, and modifying wall shear stress, vasoconstriction presents a promising strategy to disrupt tumor sustenance. These insights provide a foundation for future research focused on refining vasoconstriction techniques, ultimately working toward incorporating such methods into comprehensive cancer treatment strategies.

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