Veryst Engineering®

Engineering through the fundamentals®

Blood Damage Modeling of FDA Benchmark Nozzle

Alireza Kermani, Ph.D.
AKermani@veryst.com

Amanda Vanegas

Andrew Spann, Ph.D.

Veryst Engineering, LLC
www.veryst.com

contact@veryst.com
www.veryst.com

Introduction

- Hemolysis is the rupturing of red blood cells that releases hemoglobin into the surrounding fluid (e.g., blood plasma).
  - The increased hemoglobin could occur from a few cells that rupture completely or many cells that have an incomplete leak.
- Mechanical hemolysis is due to mechanically induced damage to red blood cells. Red blood cells, while flexible, may in some circumstances, succumb to physical shear and compression.
- Mechanical hemolysis caused by flow-induced mechanical damage to red blood cells is a concern in devices that involve transporting blood.
- CFD can improve the speed of product development by helping to find potential sources of mechanical hemolysis in devices.

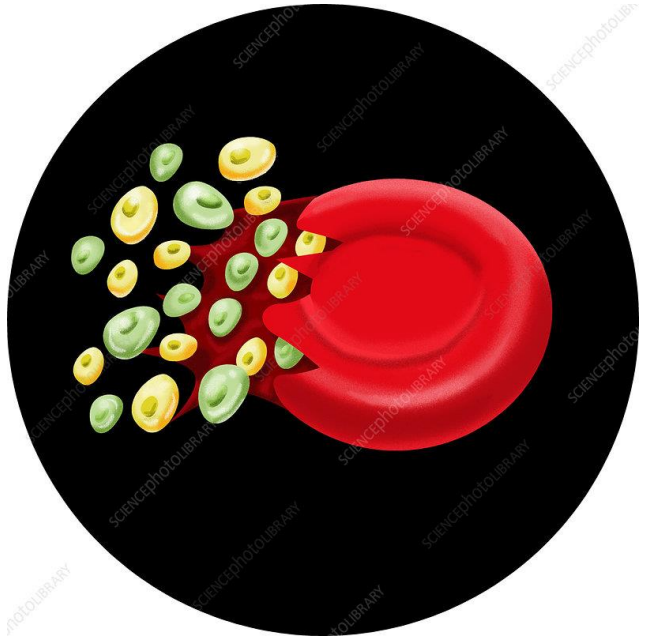


Image: https://www.sciencephoto.com/media/112913/view/ruptured-schizont-blood-cell

FDA Benchmark Nozzle

- To encourage use of simulation in regulatory submissions, the FDA released benchmark case studies with experimental data and simulation results.
- In this talk, we discuss the FDA's nozzle case study.
- CFD simulations generally match the experimental results well for flow, but less agreement was achieved from submissions with blood damage predictions.
  - Only about 1/3 of those submitting simulation predictions to the FDA study even attempted to quantify blood damage.

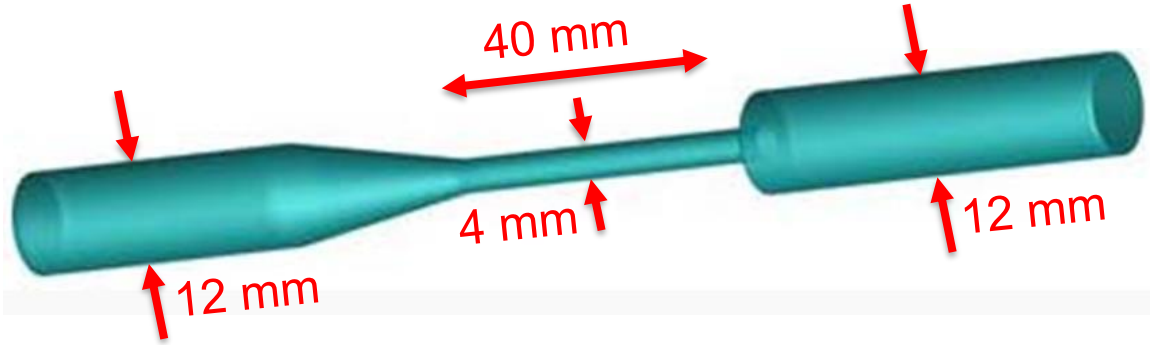


Image: https://ncihub.org/wiki/FDA_CFD/ComputationalRoundRobin1Nozzle

Blood Damage Equations

Blood Damage Model: Basic Formulation

- There are many proposed approaches for estimating blood damage.
- We are investigating a category of models which correlate hemolysis with stresses on the cells.
- These models come from fitting data to experimental measurements taken in a viscometer.
- There are several variations of these models.
- The amount of hemoglobin released by damaged red blood cells is given by an empirical power-law relation derived for constant shear stress (Giersiepen et al. in 1990):

$$H(\bar{\tau}, t) = C\bar{\tau}^{\alpha} t^{\beta}$$

  - H(%) = (released hemoglobin/total hemoglobin)
  - $\bar{\tau}$ = a scalar measuring magnitude of shear stress
  - t = exposure time to shear $\bar{\tau}$
  - α, β, C are fitted constant based on experimental data. Here we used the coefficients proposed by Zhang et al. $C = 1.228 \times 10^{-7}$, $\alpha = 1.9918$, $\beta = 0.6606$

Blood Damage Equations

- Grigioni et al. (2005) introduced “mechanical dose”, D_b, to accounts for accumulated blood damage based on the shear stress that is experienced by the red blood cells, where $dD_b = \bar{\tau}^{\alpha/\beta} dt$.
  - D_b is the mechanical dose that is accumulated over a path line
- Using mechanical dose definition Grigioni et al. originally formulated their blood damage model in a Lagrangian frame.
- Yu et al. (2017) provide the equivalent Eulerian equations:

$$\frac{\partial D_b}{\partial t} + (V.\nabla)D_b = \bar{\tau}^{\alpha/\beta}$$

$$\frac{\partial H}{\partial t} + (V.\nabla)H = c\beta D_b^{\beta-1}\bar{\tau}^{\alpha/\beta}$$

- Here H is the ratio of released hemoglobin to total hemoglobin within the red blood cells, t is time, V is velocity.
- We solved the above equations in Eulerian and Lagrangian frames.

COMSOL Simulations

Model Implementation in COMSOL

- We used SST turbulence model to solve the background blood flow.
- We used Lagrangian and Eulerian approaches to obtain blood damage estimates based on the following equations with a 2-dimensional axisymmetric model.

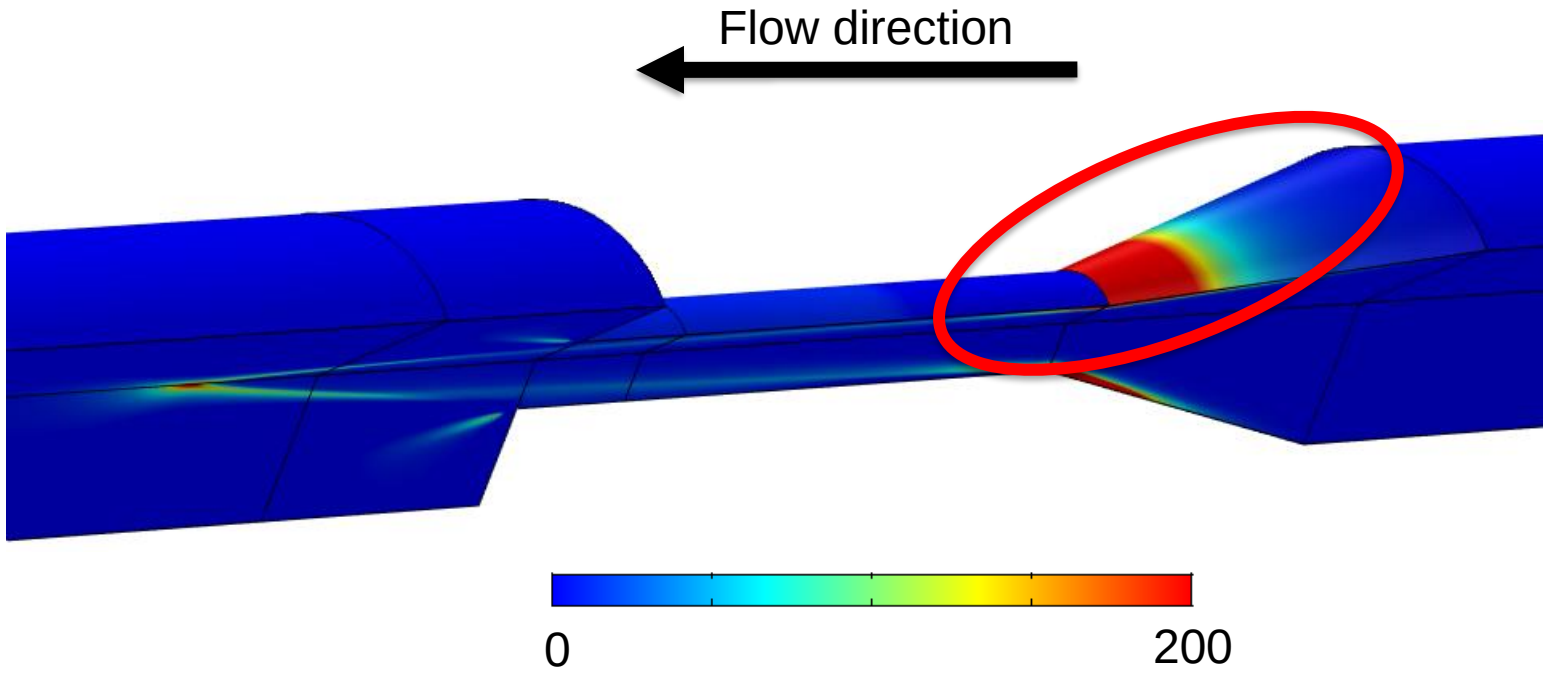
$$\frac{\partial D_b}{\partial t} + (V.\nabla)D_b = \bar{\tau}^{\alpha/\beta}$$

$$\frac{\partial H}{\partial t} + (V.\nabla)H = c\beta D_b^{\beta-1}\bar{\tau}^{\alpha/\beta}$$

- For Eulerian implementation of the above equations, we used “Transport of Diluted Species” physics in COMSOL. The right-hand sides of the equations are defined as reaction terms.
- For Lagrangian implementation, we used the auxiliary dependent variable feature of “Particle Tracing for Fluid Flow” physics in COMSOL to solve the above equations along path lines of red blood cells. We defined D_b and H as auxiliary dependent variables.

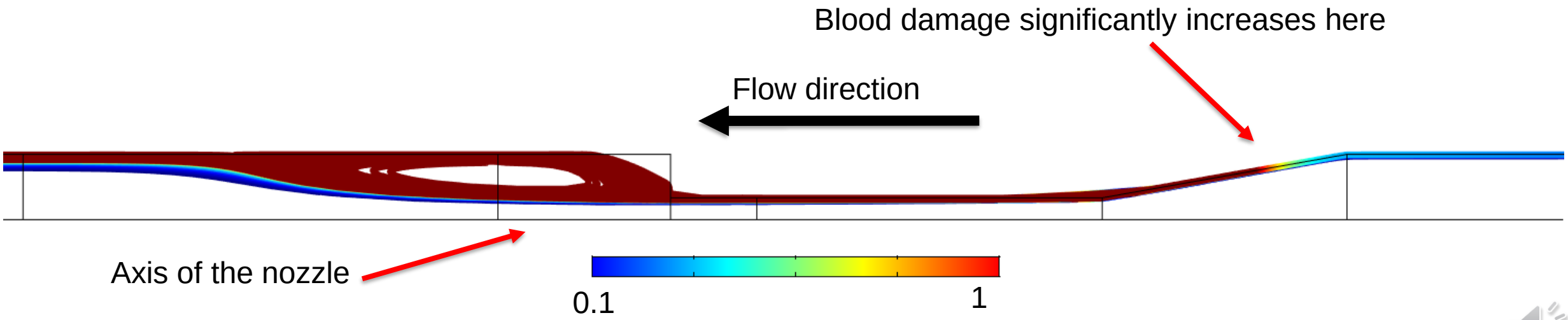
Blood Damage Distribution

- The figure shows the normalized hemolysis rate per unit length with higher values corresponding to higher localized rates of blood damage.
- Flow rate is 6 L/min; Reynolds number at the throat is 9624.
- Blood damage is mainly due to shear in the highlighted region.



Path Line

- Blood cells that their paths are shown have higher contribution to blood damage.
- The color legend corresponds to normalized blood damage. Blood damage is normalized with the total blood damage at the outlet.
- Damaged blood cells are near the wall due to the high shear. However red blood cells tend to marginate away from the walls.
  - Red blood cells have to fit through spleen regularly, which is tighter than this nozzle.



Discussion of Experimental data with Gradual Cone

- Three labs performed a total of 27 tests on the nozzle and submitted their results to FDA.
- The figure shows the average of blood damage in each lab. The reported blood damages do not agree.
- All Labs reported blood damage not significantly different from 0 for the 6 L/min gradual cone.
- The average MIH of (27 tests) with the gradual cone is 0.021±0.128. Our simulation predicts MIH of 0.18 (Eulerian) and 0.19 (Lagrangian), see the dotted line.
  - MIH= (released hemoglobin/total hemoglobin)x10^6.

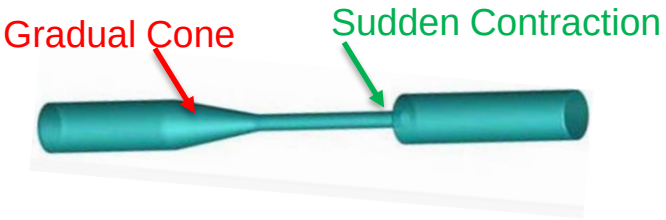
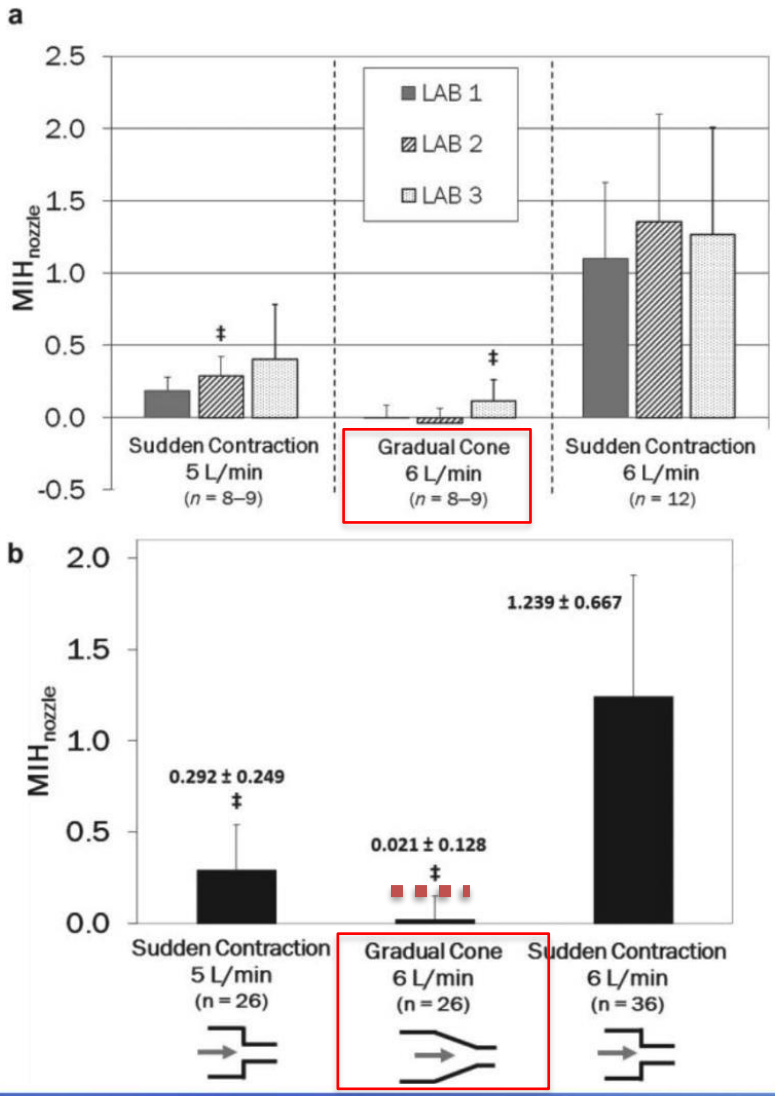


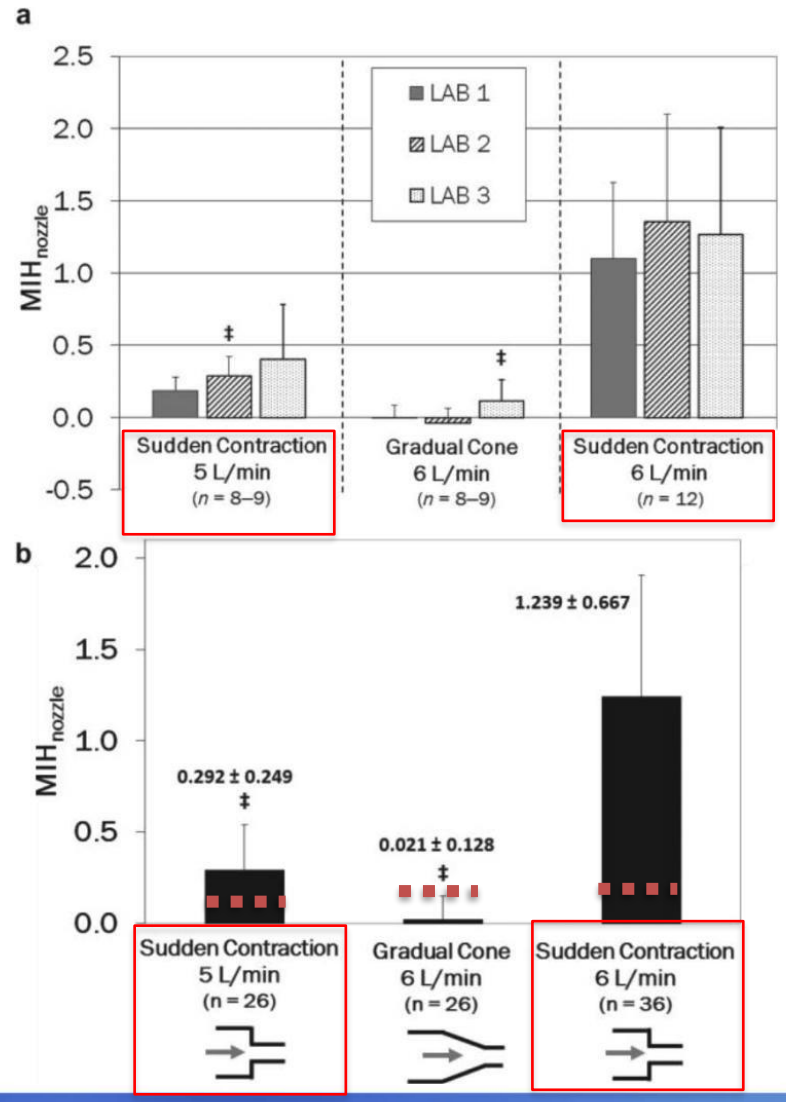
Image: Herbertson, L. H., Olia, S. E., Daly, A., Noatch, C. P., Smith, W. A., Kameneva, M. V., & Malinauskas, R. A. (2015). Multilaboratory study of flow-induced hemolysis using the FDA benchmark nozzle model.*Artificial organs*,*39*(3), 237-248.



Discussion of Experimental data with Sudden Contraction

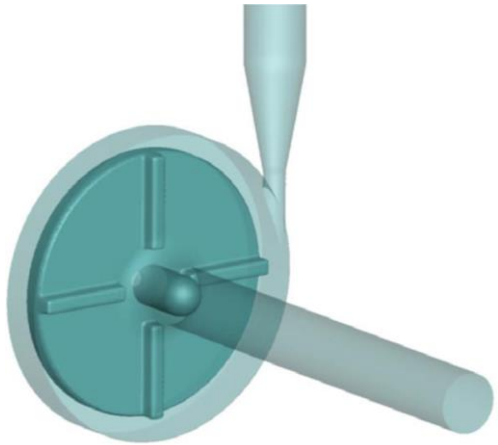
- Our simulation predicts MIH of 0.12 (dotted line) with sudden contraction at 5 L/min but does not show the sudden increase in blood damage due to an increase in flow rate from 5 L/min to 6 L/min.
- The stress-based model, including the simple power-law stress relation, does not capture the jump in blood damage that occurs from changing from the gradual cone to the sudden contraction, especially the difference when the flow is increased from 5 L/min to 6 L/min.

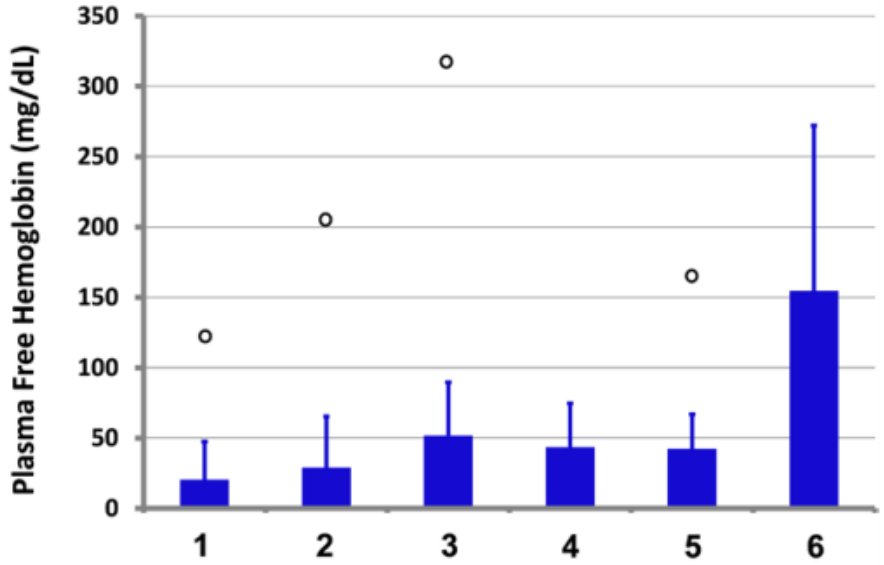
Gradual Cone Sudden Contraction



Blood Damage Tipping Point

- The figure shows hemolysis results for the FDA benchmark blood pump model at the six operating points (n = 16 replicates).
- Blood damage jumps with increase in flowrate from 6 L/min (condition 1) to 7 L/min (condition 6).





Condition #	Flow Rate (L/min)
1	2.5
2	2.5
3	4.5
4	6.0
5	6.0
6	7.0

Images: Malinauskas et al. (2017). FDA Benchmark Medical Device Flow Models for CFD Validation. ASAIO Journal: March/April 2017 - Volume 63 - Issue 2 - p 150-160

Limitations of Giersiepen Model

- The correlations used in hemolysis models were developed for shear dominated flows over short time frames (seconds or less).
  - Only valid at constant shear stress.
  - Only tested for stress $\bar{\tau}$ up to 255 Pa and time t up to 700 ms.
- It is believed that hemolysis may not occur for low stresses, possibly even approaching the 255 Pa used as the maximum stress in that experiment.
- Suggestions for hemolysis models which are more able to capture “tipping point” increases in hemolysis include multi-scale model where the stress tensor is measured based on a CFD simulation along path lines, and a separate model accounts for deformable red blood cell based on local strain distribution (see Nikfar et al. 2020).

Conclusion

- We used Lagrangian and Eulerian approaches to obtain blood damage estimates.
- CFD can improve the speed of product development by helping to find potential sources of mechanical hemolysis in devices, but there are limitations to how accurately absolute damage can be predicted.
- Stress-based power-law models may not explicitly capture “tipping point” behavior, where further increases in flow result in large increases in hemolysis.

References

- Giersiepen, M., Wurzinger, L. J., Opitz, R., & Reul, H. (1990). Estimation of shear stress-related blood damage in heart valve prostheses-in vitro comparison of 25 aortic valves. The International journal of artificial organs, 13(5), 300-306.
- Grigioni, M., Daniele, C., Morbiducci, U., D'Avenio, G., Di Benedetto, G., & Barbaro, V. (2004). The power-law mathematical model for blood damage prediction: analytical developments and physical inconsistencies. Artificial organs, 28(5), 467-475.
- Grigioni, M., Morbiducci, U., D'Avenio, G., Di Benedetto, G., & Del Gaudio, C. (2005). A novel formulation for blood trauma prediction by a modified power-law mathematical model. Biomechanics and Modeling in Mechanobiology, 4(4), 249-260.
- Taskin, M. E., Fraser, K. H., Zhang, T., Wu, C., Griffith, B. P., & Wu, Z. J. (2012). Evaluation of Eulerian and Lagrangian models for hemolysis estimation. ASAIO journal, 58(4), 363-372.
- Yu, H., Engel, S., Janiga, G., & Thévenin, D. (2017). A review of hemolysis prediction models for computational fluid dynamics. Artificial organs, 41(7), 603-621.
- Stewart, S. F., Hariharan, P., Paterson, E. G., Burgreen, G. W., Reddy, V., Day, S. W., ... & Myers, M. R. (2013). Results of FDA's first interlaboratory computational study of a nozzle with a sudden contraction and conical diffuser. Cardiovascular Engineering and Technology, 4(4), 374-391.
- Nikfar,M., Razizadeh, M., Zhang, J.,Paul, R.,Wu, Z., Liu, Y. Prediction of mechanical hemolysis in medical devices via a Lagrangian strain-based multiscale model, (2020) Aug;44(8):E348-E368