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VERIFICATION OF NUMERICAL MODELS OF HEMOLYTIC INDEX BASED ON EULERIAN AND LAGRANGIAN APPROACHES IN FDA (FOOD AND DRUG ADMINISTRATION) BENCHMARKS

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Abstract. *The change in flow caused by the insertion of clinical devices modifies the shear stress acting under blood cells, which can trigger the hemolysis process. This hemodynamic effect is related to shear stress and its exposure time, which can be modeled by a mathematical model called Hemolytic Index (HI). In this context, the computational fluid dynamics can be applied to understand the hemodynamic effects, using two approaches: Eulerian and Lagrangian. In order to compare these approaches, the study developed here reproduces the methodologies of FDA (Food and Drug Administration) Benchmarks in numerical flow models in medical devices. Based on experimental data from the literature, it was possible to verify the mathematical models used for HI. The experiment carried out consists of a numerical simulation of the blood porcine flow in a nozzle geometry, in turbulent regime for sudden-contraction inlet and gradual cone inlet conditions with different mass flow rates. From the results, it was observed high relative errors when comparing both approaches with the experiment, with greater discrepancy in relation to the sudden-contraction inlet situation. Therefore, the mathematical models presented are simple for analyzing medical devices with complex flow, in which the shear stress varies along the trajectory lines.*

Keywords: *Computational Fluid Dynamics, Hemolysis, Eulerian Approach, Lagrangian Approach.*

1. INTRODUCTION

Blood damage processes, such as hemolysis, are a major concern in clinical devices and endoprostheses. These systems when in contact with the bloodstream modify the flow pattern, causing unphysiological stress in red blood cells. The use of central venous access catheters for hemodialysis can generate regions of blood stagnation and high shear that induce platelet activation and damage red blood cells (Mareels *et al.*, 2007; Haniel *et al.*, 2019; Consolo *et al.*, 2017). Another example is the use of ventricular assist devices (VAD) to assistant patients with heart failure, which can induce damage to blood components (Zengsheng *et al.*, 2019; Tchantchaleishvili *et al.*, 2014).

Numerical simulation tools have become increasingly used in the development of medical devices. Thus, several cardiac systems can be analyzed, such as stenotic arterial models (Zhou *et al.*, 2018) and aneurysm endoprostheses (Jayendiran *et al.*, 2019; Mo *et al.*, 2018; Zhou *et al.*, 2019). However, it is necessary to validate computational fluid dynamics (CFD) simulations in order to safely predict blood damage. The Food and Drug Administration (FDA) developed reference models of typical medical device flow geometries, which were tested in several laboratories to provide experimental data to support CFD validation (Malinauskas *et al.*, 2017). Based on this methodology, several studies have sought to characterize hemolysis (Tobin and Manning, 2020; Wu *et al.*, 2019a, 2019c; Faghih *et al.*, 2021; Wang *et al.*, 2020; Song and Heuveline, 2019).

Through the CFD, the mathematical model for the hemolytic index proposed by Giersiepen *et al.* (1990), was incorporated as transport equations in an attempt to understand, from the point of view of fluid mechanics, the hemodynamic effects, through the Eulerian and Lagrangian analyses. Five models based on the Lagrangian methodology were proposed in an attempt to analyze the most appropriate approach for the study of hemolysis in cardiac systems (Taskin *et al.*, 2012). In the Lagrangian approach, the damage index is integrated along the flow lines, which allows to model the damage history suffered by the cells. On the other hand, in the Eulerian approach, the blood damage index is integrated in the control volume domain. However, according to Faghih and Sharp (2019b), this model neglects the spatial dependence of the time of exposure to shear stress, suggesting that it is suitable for the analysis of uniaxial flows with constant velocity along the streamlines. Another limitation is related to the linearization process, since the distribution of an exponent through an integral is constrained by a unitary exponent or a constant function throughout the regime, which does not include hemodynamic effects.

It is known that the hemolysis process is dependent on the shear stresses to which blood cells are exposed and the time of exposure to these stresses (Faghih and Sharp, 2019a). Furthermore, according to Goubergrits and Affeld (2004), hemolysis is dependent on cell age and the history of sublethal damage suffered. Therefore, this study aims to verify and compare the Eulerian hemolysis model and five Lagrangian mathematical models with experimental data in the literature.

The work proposed here reproduces the three flow conditions proposed by Herbertson *et al.* (2014) in a nozzle model developed by the FDA for the analysis of HI. The experiment reproduced consists of a numerical simulation of turbulent and Newtonian porcine blood in different flow rates. Through computational fluid dynamics, the values of shear stress and exposure time obtained were used for the analysis of hemodynamic effects. The mathematical models from the Eulerian and Lagrangian perspectives were compared with the modified hemolytic index values obtained by Herbertson *et al.* (2014).

2. MATERIALS AND METHODS

2.1 Geometry Model and Mesh Convergence Test

The numerical simulations performed were based on an FDA nozzle model, as shown in Figure 1. This model is an idealized and simplified medical device, consisting of a nozzle, which shares characteristics of blood-carrying medical devices, such as blood tubes, hemodialysis sets, catheters, cannulas, syringes and hypodermic needles. The geometry was designed to include accelerated flow, decelerated flow, shear stress and velocity variations, and recirculating flow, which may be related to blood damage in medical devices (Stewart *et al.*, 2012).

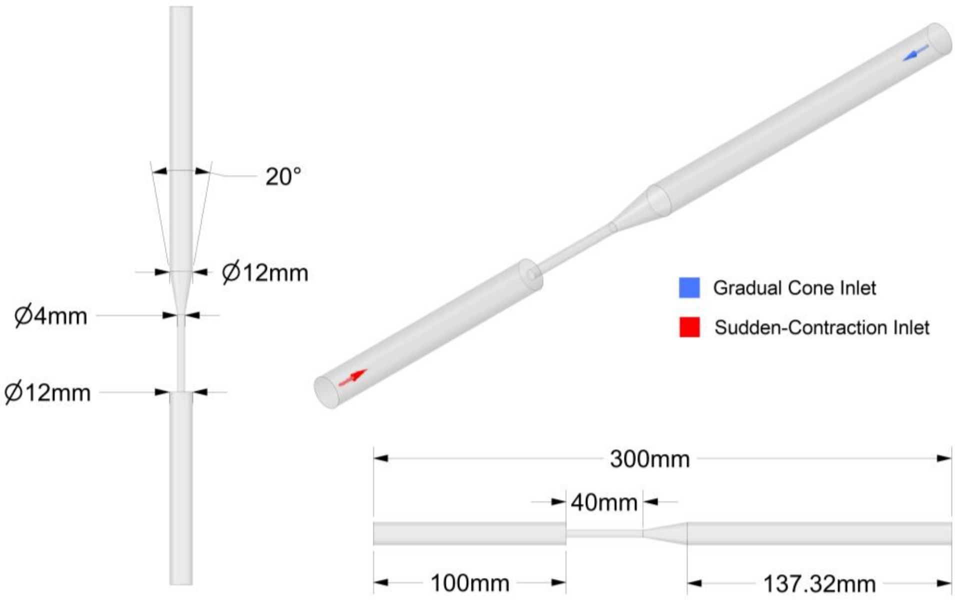

Figure 1. Fluid domain of FDA nozzle.

ANSYS-Fluent® 20.1 software (ANSYS Inc., Lebanon, NH, USA) was used to perform the spatial discretization and the solution of the Navier-Stokes equations. The transport equations for the Eulerian hemolytic index were implemented using user-defined functions (UDF) in C language.

Five finite volume meshes was performed through the grid convergence test based on the ASME V&V 20-2009 standard for all conditions studied. The meshes were developed from first-order quadrilateral and prismatic elements, with a refinement of nine layers close to the wall. Different points in the domain were monitored, through the established criterion of minimum GCI error of 5% of the HI between the meshes. Thus, when this requirement was met between two consecutive meshes, the previous one was chosen. This mesh has 398627 elements, 405038 nodes and average skewness of 0.11676.

2.2 Fluid Rheology and Boundary Conditions

The simulation used porcine blood with viscosity (μ) of 0.00406 Pa.s and density (ρ) equal to 1040 kg/m³ (Herbertson *et al.*, 2014).

To calculate the shear stress, Newton's Law of Viscosity was used, which determines that, at a given shear stress (τ), the fluid strain rate ($\partial u/\partial y$) is proportional to viscosity (μ), as shown:

$$\tau(y) = \mu \, \frac{\partial u}{\partial y}, \tag{1}$$

As a turbulence model, the k-ω SST (Shear Stress Transport) model was adopted. This model presents the advantages of the k-ω formulation close to the walls with the free flow independence of the k-ε model outside the boundary layer.

To experimentally evaluate the hemolysis process, in the study by Herbertson *et al.* (2014) an in vitro blood damage test was performed in three different laboratories, using bovine and porcine blood in a simple nozzle model developed by the FDA. To determine how different blood flow parameters and properties affect hemolysis in devices, three conditions were evaluated: sudden-contraction inlet with a blood flow rate of 8.33×10^{-5} m³/s, gradual cone inlet at 1.00×10^{-4} m³/s, and sudden-contraction inlet at 1.00×10^{-4} m³/s. According to the data provided in this study, at the inlet of each condition, the mass flow of 8.42×10^{-5} m³/s, 9.90×10^{-5} m³/s and 1.01×10^{-4} m³/s were defined. The zero pressure condition were used in the outlets and the non-slip condition in the walls, with a roughness of 3×10^{-7} m. For HI, it was defined null value at inlet, and zero flux at outlet and wall.

For the analysis of the Lagrangian approach, 1388 and 685 particles were sown in the flow for the cases of sudden-contraction inlet and gradual cone inlet, respectively.

The Coupled algorithm was used for velocity-pressure coupling. For the discretization of gradients and pressure, the Least Squares Cell Based and Second Order algorithms were adopted, respectively. The momentum and the Users Scalars (time of residence and hemolytic index) were discretized using the First Order Upwind method. On the other hand, for the turbulent kinetic energy and the specific dissipation rate, the Second Order Upwind method was used. As a convergence condition, a value of 10^{-6} was applied to the residuals for all calculations.

After solving the numerical methods, the calculations for the analysis of hemolysis were performed using the MATLAB® R2019a software, defined by their flow-weighted average. In this process, a mathematical model in the Eulerian approach and five models in the Lagrangian approach were implemented through time, shear stress and flow data obtained in the post-processing of the simulations.

2.3 Numerical Models of Hemolytic Index (HI)

The numerical models used to estimate the hemodynamic effects of hemolysis were proposed by Giersiepen *et al.* (1990) from experiments. For hemoglobin (Hb) release by red blood cells:

$$HI(\%) = \frac{\Delta Hb}{Hb} \times 100 = C\, t_{exp}^{\alpha}\, \tau^{\beta}, \tag{2}$$

where, τ is shear stress, t_{exp} is exposure time and ΔHb is plasma free hemoglobin.

According to Ding *et al.* (2015), the constants for power-law C, α and β for porcine blood are 6.701×10^{-4}, 1.0981 and 0.2778, respectively.

2.3.1 Eulerian Approach

As stated by Taskin *et al.* (2012), the scalar transport equation for hemolysis, considering the Eulerian approach, is expressed as:

$$\frac{d(\Delta Hb')}{dt} + v\rho \cdot \nabla\left(\Delta Hb'\right) = S, \tag{3}$$

where,

$$\Delta Hb' = \Delta Hb^{1/\alpha}, \tag{4}$$

and S is the source term defined as:

$$S = \rho\, (Hb\, C\, \tau^{\beta})^{1/\alpha}, \tag{5}$$

2.3.2 Lagrangian Approach

The five Lagrangian mathematical models exposed by Taskin *et al.* (2012) were used for this analysis. The first one was used by several researchers (Chan *et al.*, 2002; Yano *et al.*, 2003; Song *et al.*, 2004). The mathematical equation considers blood damage as the average of the streamlines in the output integrated for each time interval, starting from the power-law, as shown:

$$HI1 = \int_{inlet}^{outlet} C\, dt_{exp}^{\alpha}\, \tau^{\beta} = \sum_{inlet}^{outlet} C\, \Delta t_{exp}^{\alpha}\, \tau^{\beta}, \tag{6}$$

The second one calculates accumulated damage by integrating the time derivative of the power-law method (Zimmer *et al.*, 2000; Lim *et al.*, 2001; Grigioni *et al.*, 2002):

$$HI2 = \sum_{inlet}^{outlet} \alpha\, C\, t_{exp}^{\alpha-1}\, \tau^{\beta}\, \Delta t_{exp}, \tag{7}$$

Garon and Farinas (2004) developed the third one as shown in Eq. (8), based on the sum of this linearized damage.

$$HI3 = C \left(\sum_{inlet}^{outlet} \Delta t\, \tau^{\beta/\alpha}\right)^{\alpha}, \tag{8}$$

The fourth one was developed by Grigioni *et al.* (2005), including the dose of physical mechanisms D, acting along the blood cell trajectory in the same way as the second method, as follows:

$$HI4 = \sum_{inlet}^{outlet} \alpha\, C \left[\sum_{j=1}^{i} \tau(t_j)^{\frac{\beta}{\alpha}} \Delta t_j + D(t_0)\right]^{\alpha-1} \tau(t_j)^{\beta/\alpha}\, \Delta t_i, \tag{9}$$

where,

$$D = t_{exp}\, \tau^{\beta/\alpha}, \tag{10}$$

Finally, the fifth one proposed by Goubergrits and Affeld (2004) considers the history of blood damage like the previous method, assuming that the hemodynamic effect is a function of cell age and sublethal cell damage, so that the current damage is independent of how the damage to existing blood arose. Thus, it is defined as:

$$HI5(t+\Delta t) = C \left(t_{eff}+\Delta t\right)^{\alpha} \tau(t+\Delta t)^{\beta}, \tag{11}$$

where, t_{eff} is:

$$t_{eff} = \left(\frac{HI5(t)}{C\, \tau(t+\Delta t)^{\beta}}\right)^{1/\alpha}, \tag{12}$$

3. RESULTS AND DISCUSSION

Table 1 shows the results found for the Eulerian approach and the five Lagrangian models, compared to the average modified hemolysis index values between three laboratory experiments (Herbertson *et al.*, 2014).

Table 1. Comparison between the Eulerian and Lagrangian approaches with experimental data.

HI	**Sudden-contraction inlet, 8.33×10^{-5} m³/s**	**Gradual cone inlet, 1.00×10^{-4} m³/s**	**Sudden-contraction inlet, 1.00×10^{-4} m³/s**
Experimental (1)	0.292000	0.021000	0.021000
HI Eulerian	0.021150	0.023679	0.024448
HI1 Lagrangian	2.035674	0.091390	0.322060
HI2 Lagrangian	0.000121	0.000004	0.054233
HI3 Lagrangian	0.071954	0.010210	0.009313
HI4 Lagrangian	0.061590	0.006405	0.007532
HI5 Lagrangian	0.071954	0.010210	0.009313

(1) Herbertson *et al.* (2014)

Figure 2 shows the relative errors in percentage between the numerical models and the experimental data. As noted, the first and second Lagrangian models showed greater errors in relation to the data obtained by Herbertson *et al.* (2014), proving to be unsuitable for this application. On the other hand, the third and fifth Lagrangian models showed fewer relative errors than the Eulerian one, in the case of sudden-contraction inlet. As for the case of gradual cone inlet, it was observed that the Eulerian model presented a closer approximation, possibly because in this condition the fluid presents smaller turbulence, with less shear stress variations along the flow line.

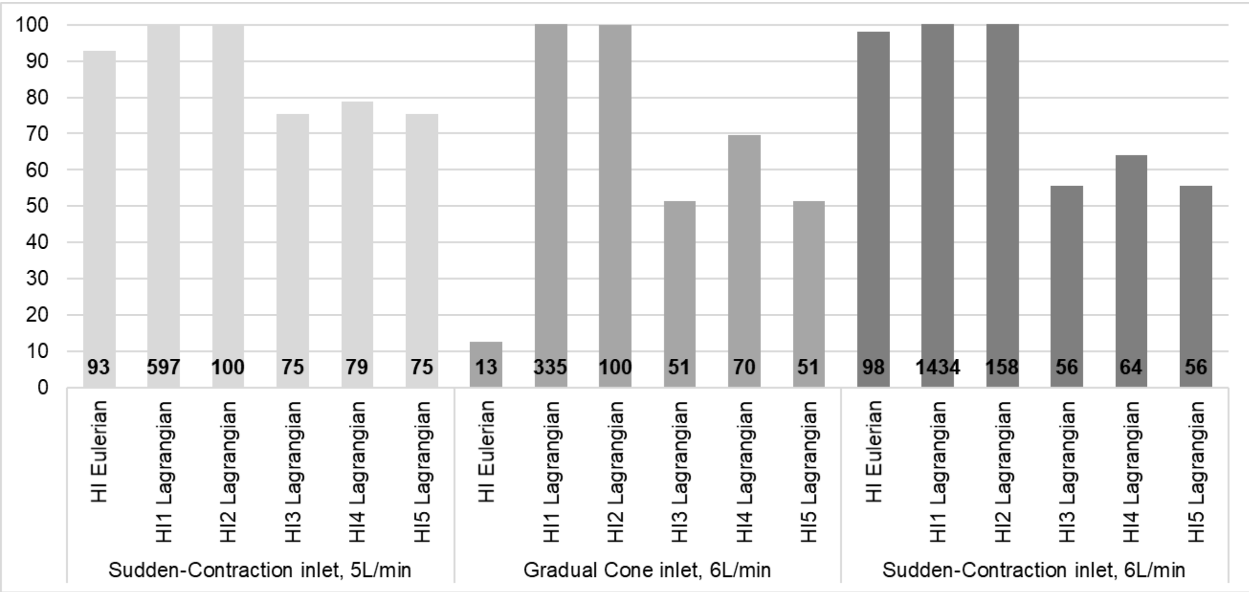

Figure 2. Graph of relative errors (%) of numerical HI values compared to experimental data.

Figure 3 shows the variation in the value of the hemolytic index during the trajectories of the particles in the three conditions studied. Thus, it was found that the case of sudden-contraction inlet with higher flow presented the highest HI values. This may occur due to the elevated velocity and turbulence developed (Figure 4), which trigger a greater shear stress.

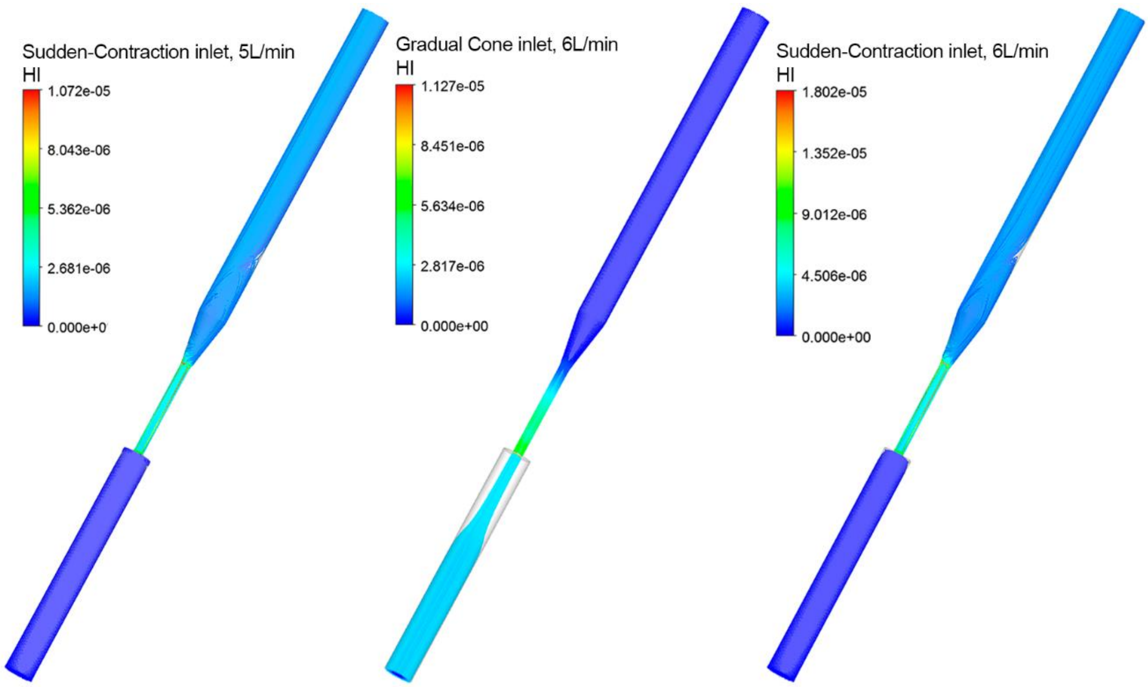

Figure 3. HI contour lines on particle trajectories.

In Figure 4, the velocity of the particles along the profile was verified, so that it was possible to observe a large recirculation after the contraction and a greater turbulence for cases of sudden-contraction at the inlet.

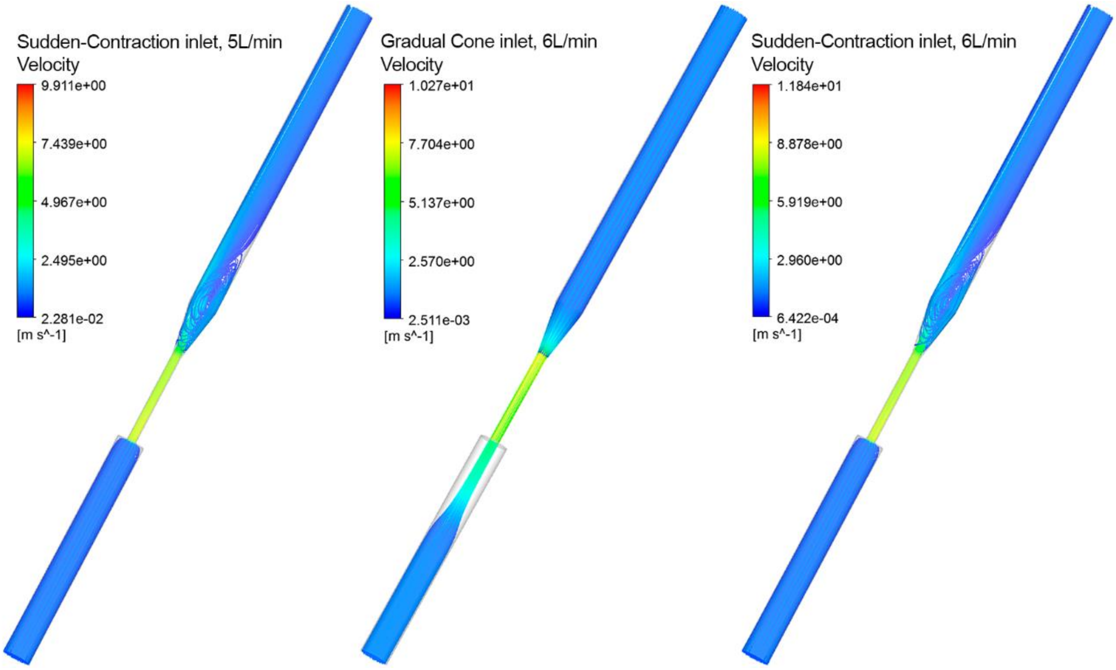

Figure 4. Velocity contour lines on particle trajectories.

As the HI can be described as a function of the shear stress and its residence time, it can be seen its variation along the geometry in Figure 5. It was observed that the residence time was higher in the first and third cases, which have more recirculating flow.

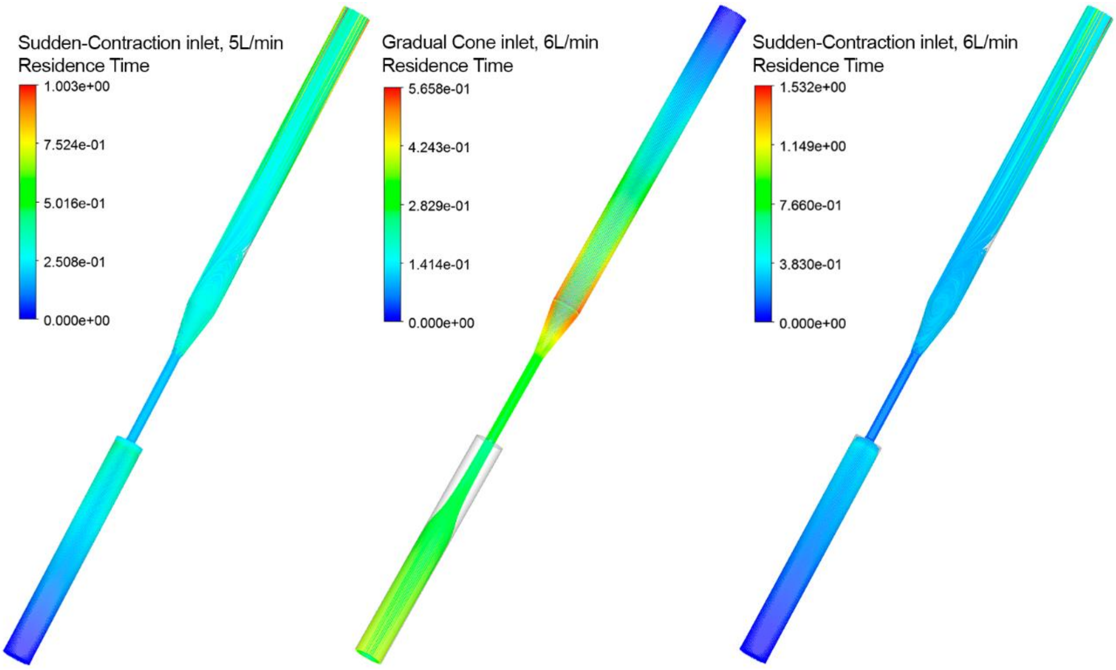

Figure 5. Residence time contour lines on particle trajectories.

Most of the results found showed high relative error, which may have been due to the turbulence model used, since the central line flow in the inlet and throat regions was laminar in these regions (Stewart *et al.*, 2012). Therefore, the formulation used was probably not accurate in predicting the shear stresses in the recirculation zones downstream of the sudden expansion, which may have been responsible for making the values of the inlet conditions with sudden-contraction more discrepant.

According to Wu *et al.* (2019b), the influence of turbulent intensity on flow and hemolysis is small for the gradual inlet cone configuration. However, for sudden-contraction inlet, this influence is considerable, reaching up to 38.5% for hemolysis. In this study, with increasing turbulent intensity, there was a difference in hemolysis of up to 40%. In the study by Taylor *et al.* (2016), it was also verified that the turbulent flow condition with sudden-contraction inlet causes substantially higher Reynolds stresses when compared to a gradual contraction.

Herbertson *et al.* (2014) calculated the modified hemolytic index as a function of hematocrit of the blood, volume, total hemoglobin concentration, flow rate and variation in plasma free hemoglobin concentration, in addition to experiment time. This is a limitation of the model adopted (Giersiepen *et al.*, 1990), which calculates HI as a relation of free hemoglobin and total hemoglobin concentration as a function of shear stress and exposure time. Thus, it is necessary to investigate more complex models to analyze the hemolysis process in cardiac assistance systems, such as the one proposed by Craven *et al.* (2019).

4. CONCLUSION

In order to verify the mathematical models of the Eulerian and Lagrangian approaches presented by Taskin *et al.* (2012), the experiment by Herbertson *et al.* (2014) on an FDA nozzle model was reproduced numerically.

From the results, high relative errors were verified when comparing both approaches with the experiment, in which the first Lagrangian method presents greater discrepancy. Furthermore, the cases of sudden-contraction inlet presented more dissonant values in relation to the experimental values than the cases of gradual inlet cone, since they have flow with recirculation zones due to the higher adverse pressure gradient.

This work demonstrated that the studied mathematical models are simple for the analysis of medical devices with complex flow, in which the shear stress varies in the trajectory lines. Furthermore, the model used to characterize the transition from laminar to turbulent regime was not sufficiently accurate for the problem under analysis. Thus, it is necessary to develop more elaborate models to analyze the hemolysis process in more complex applications.

5. ACKNOWLEDGEMENTS

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