Are Non-Newtonian Effects Important in Hemodynamic Simulations of Patients With Autogenous Fistula?

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Given the current emphasis on accurate computational fluid dynamics (CFD) modeling of cardiovascular flows, which incorporates realistic blood vessel geometries and cardiac waveforms, it is necessary to revisit the conventional wisdom regarding the influences of non-Newtonian effects. In this study, patient-specific reconstructed 3D geometries, whole blood viscosity data, and venous pulses postdialysis access surgery are used as the basis for the hemodynamic simulations of renal failure patients with native fistula access. Rheological analysis of the viscometry data initially suggested that the correct choice of constitutive relations to capture the non-Newtonian behavior of blood is important because the end-stage renal disease (ESRD) patient cohort under observation experience drastic variations in hematocrit (Hct) levels and whole blood viscosity throughout the hemodialysis treatment. For this purpose, various constitutive relations have been tested and implemented in CFD practice, namely Quemada and Casson. Because of the specific interest in neointimal hyperplasia and the onset of stenosis in this study, particular attention is placed on differences in nonhomeostatic wall shear stress (WSS) as that drives the venous adaptation process that leads to venous geometric

evolution over time in ESRD patients. Surprisingly, the CFD results exhibit no major differences in the flow field and general flow characteristics of a non-Newtonian simulation and a corresponding identical Newtonian counterpart. It is found that the vein's geometric features and the dialysis-induced flow rate have far greater influence on the WSS distribution within the numerical domain. [DOI: 10.1115/1.4035915]

Keywords: hemodynamics, non-Newtonian flow, wall shear stress (WSS), neointimal hyperplasia, computational fluid dynamics (CFD), arteriovenous fistula

1 Introduction

Arteriovenous fistulae are surgical connections between a vein and an artery at an anastomosis to provide adequate flow rate to perform chronic hemodialysis on ESRD patients. This intrusive manipulation to the natural homeostatic state of the venous system, however, creates multiple biomechanical stimuli that trigger adaptive responses leading to the development of neointimal hyperplasia and stenosis [1–6], which may ultimately lead to eventual stenosis and access failure in these patients (Fig. 1).

In this article, computational fluid dynamics is used to noninvasively study the hemodynamic environment of the autogenous dialysis access in renal failure patients. We wish to take particular note of the application of non-Newtonian models in CFD practice applied to this specific patient cohort. In particular, there is a need to revisit the relative merits of constitutive models as the matter has been a center of controversy in the field of biofluid mechanics for decades and many authors have contradictory approaches toward the topic. The conventional wisdom models blood as follows [7,8]:

- $d \sim r$ (e.g., capillaries): multiphase fluid;
- $d > r$ (small/medium sized vessels): non-Newtonian fluid;
- $d \gg r$ (large vessels): Newtonian fluid;

where d represents the vessel diameter and r denotes the red blood cell (RBC) effective radius. In the first category, the flow has to be modeled as a multiphase continuum, whereas in the last two categories, a single-phase continuum model is adequate. Nevertheless, there are many others who believe that the non-Newtonian nature of blood must always be accounted for regardless of the geometry or the flow characteristics of the vessel being observed. For example, Taylor and Humphrey [9] mentioned the potential importance of non-Newtonian effects on hemodynamics in complex domains. On the other hand, Refs. [7] and [10–13] are all in favor of using the Newtonian flow assumption, while many others [14–25] highlight the differences between the two assumptions in various different scenarios.

In this article, the authors intend to thoroughly scrutinize the non-Newtonian effects present in the hemodynamics for ESRD dialysis access. Section 2 discusses the influence of hematocrit level on overall blood viscosity and the constitutive relations that encapsulate hematocrit as an independent variable. In Sec. 3, these viscosity models are applied to computational models of patient-specific hemodynamics to observe the potential dissimilarities brought about by the implementation of non-Newtonian models in CFD practice which would guide the comprehensive conclusions presented thereafter.

2 Blood Rheology and Hematocrit

For blood, shear rate ($\dot{\gamma}$) is the most important hemorheological parameter (HRP). This is due to the fact that blood is shear-thinning and its apparent viscosity decreases as $\dot{\gamma}$ increases² [26]. Shear rate is defined by

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²The shear rate typically varies from 0 to more than 1000 s^{-1} during every cardiac cycle.

Fig. 1 A very severe cephalic arch stenosis detected in a patient under observation in our study at 12 months postaccess surgery. The blood flow is from right to left. Two-dimensional reconstructed geometry (top) and the 3D reconstructed geometry (bottom).

Fig. 2 Hematocrit and resulting apparent viscosity (cP) comparison between normal and ESRD patients blood samples. Red dots represent the ESRD patients under observation, while blue dots are representative of a healthy population.

Fig. 3 Postdialysis Hct and consequent apparent viscosity increase through time for subject 11 at 0, 3, and 12 months

$$\dot{\gamma} = 2\sqrt{D_{II}} \quad (1)$$

in which D_{II} is the second invariant of the symmetric part of the velocity gradient tensor. In a two-dimensional tensor notation

$$D_{II} = \sum_{i,j=1}^2 S_{ij}S_{ij} \quad (2)$$

in which S_{ij} is defined as

$$S_{ij} = \frac{1}{2} \left(\frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} \right), \quad i, j = 1, 2 \quad (3)$$

Hematocrit (Hct) level is another important parameter in blood rheology that represents the volume percentage of the RBC in a sample. In a normal population, Hct ranges roughly from 40% to 50%. In the patient cohort at hand, however, the Hct distribution tends to be very different than would be expected of a normal population. The distinct distribution of Hct in this patient population compared to a normal population along with its effect on whole blood viscosity is illustrated in Fig. 2. It can be seen that Hct in the ESRD patients ranges from 23% to 45%. Additionally, it was reported that, due to the mechanical trauma caused to the RBC by the dialysis pump and the resulting rouleaux formation, Hct levels are constantly changing in a time scale of months in every renal failure patient on chronic hemodialysis (consult [27] for longitudinal information). This is illustrated in Fig. 3, where the blood viscosity derived for subject 11 are depicted at three time intervals relative to the time of access creation. What can be inferred from Fig. 3 is (1) the direct relationship between Hct value and blood viscosity³ and (2) that the patient-specific blood viscosity is constantly changing through time during the hemodialysis treatment. These are signs that suggest non-Newtonian effects might play a notable role in determining hemodynamics, especially in patients enduring nonhomeostatic conditions.

For the purpose of this substudy, two ESRD test subjects were chosen, one with a long cephalic arch and a large arch angle (Fig. 4), and the other with a short cephalic arch and a small arch angle (Fig. 5). This choice of patients endowed us with the ability to simultaneously assess the relative effects of vessel geometry on

³Quemada also finds blood apparent viscosity to be an increasing function of hematocrit [28]. This increase is due to rouleaux density, cell-cell interaction, etc. [26,29].

Fig. 4 Reconstructed cephalic vein geometry for subject 27 at 3 months. Venogram (top), 2D (middle), and the 3D geometry (bottom).

Table 1 Viscosity models considered for patient-specific hemodynamics. In this notation, $\phi = \text{Hct}$. Consult [30].

Constitutive model	Effective μ
Newtonian fluid	Constant patient-specific asymptotic viscosity (μ)
Quemada	$\mu(\dot{\gamma}, \phi) = \mu_F \left(1 - \frac{1}{2} \frac{k_0 + k_\infty \dot{\gamma}^{\frac{1}{2}}}{1 + \dot{\gamma}^{\frac{1}{2}}} \phi \right)^{-2}$
Walburn–Schneck	$\mu(\dot{\gamma}, \phi) = k(\phi) \dot{\gamma}^{n(\phi)-1}$ where, $k = C_1 e^{C_2(\phi)}$ and $n = 1 - C_3(\phi)$
Casson	$\mu(\dot{\gamma}, \tau_y(\phi)) = \left[\left(\eta^2 \frac{\dot{\gamma}^2}{4} \right)^{\frac{1}{4}} + \sqrt{\frac{\tau_y(\phi)}{2}} \right]^{\frac{2}{ \dot{\gamma} }}$ where, $\tau_y = 0.1(0.625\phi)^3$ and $\eta = \mu_F(1 - \phi)^{-2.5}$
Modified cross	$\mu(\dot{\gamma}) = \mu_\infty + \frac{\mu_0 - \mu_\infty}{[1 + (\lambda \dot{\gamma})^b]^a}$
Carreau–Yasuda	$\eta(\dot{\gamma}) = \eta_\infty + (\eta_0 - \eta_\infty) [1 + (\lambda \dot{\gamma})^a]^{\frac{(n-1)}{a}}$

Table 2 Patient-specific Quemada HRP for subject 27 at 3 months

Parameter	Value
k_0	3.74 ± 0.0049
k_∞	1.038 ± 0.0052
$\dot{\gamma}_c$ (s^{-1})	204.25
μ_F (Pa·s)	0.00139
ϕ	$32.2\% \pm 0.21\%$

Table 3 Patient-specific Quemada HRP for subject 12 at 3 months

Parameter	Value
k_0	4.77 ± 0.0051
k_∞	1.64 ± 0.0046
$\dot{\gamma}_c$ (s^{-1})	217.33
μ_F (Pa·s)	0.00153
ϕ	$28.1\% \pm 0.08\%$

Fig. 5 Reconstructed cephalic vein geometry for subject 12 at 3 months. Venogram (top) 2D (middle), and the 3D geometry (bottom).

Fig. 6 Quemada model fitted to viscometry data of subject 27 at 3 months; $R^2 = 0.999929$

Fig. 7 Quemada model fitted to viscometry data of subject 12 at 3 months; $R^2 = 0.999964$

Fig. 8 Subject 12 at 3 months postdialysis patient-specific cardiac waveform obtained from the Doppler velocimetry measurements performed and interpreted by interventional radiologist at the time of venogram (top) and the curve fitted waveform used as the inlet condition for patient-specific CFD simulation (bottom)

the patient-specific hemodynamics. Blood samples drawn from these patients were tested for RBC content and also underwent a viscometry test (Brookfield programmable DV-II+cone-plate viscometer interfaced with RHEOLAC software produced from Brookfield Engineering Laboratories, Inc., Mt Prospect, IL [27]). In order to capture the non-Newtonian effects of blood, the obtained viscometry data should be fitted to non-Newtonian models with the aim of determining the HRP for each patient. These parameter values for the non-Newtonian viscosity models are generated using a least-squares regression to the empirical rheological data.⁴

⁴We have used a built-in evolutionary algorithm of the predefined “nonlinear model fit” function of Wolfram Mathematica V.10.2.0.

Fig. 9 Generated cephalic vein finite-element mesh for subject 27 at 3 months

Fig. 10 Streamlines at the last cardiac cycle of the simulation, $t/t_p = 1$, for subject 27. The colors represent velocity magnitude.

Various non-Newtonian models have been developed in the literature for which the reader is recommended to consult [15,30]. The choice of non-Newtonian model may be based on several factors. In the present case, where patient-specific viscometry data are available, the preferred model is one which (1) was developed specifically, or at least has been adapted, for blood's rheological parameters, such as hematocrit, (2) contains the minimum number of parameters that facilitate a good fit to the actual viscosity data [16], and (3) are amenable to implementation in a CFD code. The model that best meets these criteria is that due to Quemada [28,31,32]. Casson [15,33] has the additional virtue that, unlike

the others, it incorporates the yield stress as an additional parameter. Other non-Newtonian models and their mathematical description are presented in Table 1. HRP obtained from Quemada curve fitting for the two test subjects are presented in Tables 2 and 3, and the resulting fitted curves are illustrated in Figs. 6 and 7. For Casson, the incorporation of Hct is facilitated via the relationships: $\tau_y = 0.1(0.625\phi)^3$, the yield stress, and $\eta = \mu_F(1 - \phi)^{-2.5}$, the asymptotic viscosity. These terms can be readily calculated by substituting a patient-specific hematocrit value.

In Table 1, μ_F is the solvent medium (plasma) viscosity, which is a patient-specific quantity but varies very little from one patient to another. $\dot{\gamma}_r$ is the reduced shear rate equal to $\dot{\gamma}/\dot{\gamma}_c$, in which $\dot{\gamma}_c$ is the critical shear rate taken to be equal to U/l , which is the ratio between the inlet velocity and the inlet diameter [34–36]. k_0 and k_∞ are the lower and upper Quemada limit viscosities, respectively, which are related to the RBC solute particle shape.

3 Implementation in CFD

Patient-specific venograms and Doppler velocimetry are performed simultaneously by an interventional radiologist and are used to reconstruct the geometries and inlet velocity profiles, respectively [30,37]. In Figs. 4 and 5, sample venograms and the generated geometries are illustrated for subjects 27 and 12, respectively, both at 3 months postaccess surgery. This is known as the time of maturation, when the fistula is ready to be used for

dialysis access. Intravascular ultrasound (IVUS) or magnetic resonance angiography (MRA) imaging can be used as the basis for three-dimensional geometry reconstruction, but are not widely clinically available and are not feasible for large patient cohorts. Consequently, to be able to regenerate the three-dimensional computer-aided design (CAD) models, two-dimensional geometries were rotated 360 deg azimuthally along their respective centerline to reconstruct the three-dimensional geometries shown in Figs. 4 and 5. The resulting three-dimensional geometries seem to represent the actual veins with relatively fine anatomical-luminal details.

COMSOL Multiphysics CFD solver and postprocessor were utilized in this study. Using a Galerkin–Petrov unsteady solver, conservation of mass and momentum are solved as follows:

$$\rho(\partial_t \mathbf{u} + \mathbf{u} \cdot \nabla \mathbf{u}) = -\nabla p + \nabla \cdot [\mu(\nabla \mathbf{u} + (\nabla \mathbf{u})^T)] + \rho \mathbf{f} \quad (4)$$

$$\nabla \cdot \mathbf{u} = 0 \quad (5)$$

in which ρ is the density, $\mathbf{u}$ is the fluid velocity vector, p is the pressure, μ is the apparent viscosity, which is the focus of this study, and $\mathbf{f}$ is the summation of body forces acting on the fluid. The third term on the right-hand side is the contribution to viscous effects that arises from non-Newtonian effects. For Newtonian cases, this term is set to zero in the nonstress formulation.

Fig. 11 Cross-sectional velocity contours superimposed on velocity magnitude pseudo-color plots at three different locations for three simulations

Walls are taken to be impermeable and rigid with no-slip boundary condition applied throughout the domain. A zero pressure Dirichlet and a zero divergence boundary condition are applied at the outlet, and the unsteady simulation starts from rest. Blood flow in the cephalic vein is laminar and can be taken to be almost steady under homeostatic conditions. Postaccess surgery, however, the introduction of the arterial flow into the venous system leads to pulsation becoming appreciable in the vein. Therefore, the inlet cardiac pulse waveform is taken from the patient-specific Doppler measurement. The Doppler-measured inlet pulse wave functions for subject 12 are depicted in Fig. 8 for example. The period of pulsation in the cephalic vein as read and interpreted by the interventional radiologist for subjects 12 and 27 are $t_p = 0.7$ s and $t_p = 0.91$ s, respectively. Computations are performed using a numerical grid consisting of ten layers of boundary-layer elements, 1.2 M free tetrahedral domain elements, and 216 K boundary elements (Fig. 9) obtained from a mesh independence study to provide sufficient spatial resolution that ensures verified numerical results. The unsteady solver was run for six complete cardiac cycles for each subject-specific case considered here. The time step size of 10^{-4} s was found to be accurate and computationally efficient from a temporal resolution study. The same patient-specific inlet cardiac waveform profile was considered for the companion non-Newtonian simulations. Newtonian viscosity is constant and is taken to be equal to the asymptotic viscosity for high shear rates. For subject 27 and subject 12, this value is equal to $\mu = 0.00269$ Pa·s and $\mu = 0.00287$ Pa·s, respectively.

In order to quantify the differences between CFD results based on the Newtonian and non-Newtonian models, three simulations were performed for each of the two patients according to the following protocol:

- (1) Newtonian simulations: The asymptotic constant viscosity values at high shear rates obtained from viscometry data for subjects 27 and 12 are used.

- (2) Non-Newtonian simulation: Quemada's shear-thinning model incorporated with the HRP generated using a least-squares regression technique (Figs. 6 and 7, Tables 2 and 3).
- (3) Non-Newtonian simulation: Casson's viscoplastic model incorporated with the yield stress and asymptotic viscosity terms directly calculated utilizing Hct as an independent variable.

4 Results and Discussion

The results of both sets of simulations are visually and qualitatively comparable and the differences are inconspicuous. In order to spot the most perceptible discrepancies, streamfunction plots, WSS, and time-averaged wall shear stresses (TAWSSs) are depicted in Figs. 10–14 for both subjects studied herein. A closer observation of the results can highlight some detectable differences for comparison purposes, while we reiterate that the inconsistencies between subject-specific Newtonian and non-Newtonian three-dimensional hemodynamic CFD simulations considered here are insignificant. The small difference between the three CFD simulations are strong indications that the errors in model parameter estimation in the curve fittings and the underlying experimental errors in the viscometry tests are all of secondary importance, thereby mitigating the need to quantify the confidence intervals of the viscometry tests and non-Newtonian models fitted parameters.

Because of the higher viscosity at low shear rates, non-Newtonian flows are less prone to form recirculation zones near walls and eddies in general. Following the same line of reasoning, one would expect that the reversed flow regions occurring in a non-Newtonian flow field would be smaller in size and slower in velocity than that of a Newtonian flow. Figure 10 illustrates the streamlines resulting from the three simulations for subject 27. Close to the inlet and adjacent to the upper wall, a recirculation

Fig. 12 Streamlines at the sixth half cycle time $t/t_p = 0.5$ for subject 12. A recirculation zone close to the inlet in the Newtonian flow is absent in the two non-Newtonian counterparts.

zone forms in the Newtonian simulation that is absent in the same location of the Quemada simulation and weaker in the Casson counterpart. This effect occurs in two more indicated recirculation zones within the downstream domain, pointing to the fact that non-Newtonian viscous effects are slightly damping the violent flow behavior brought about by geometrical peculiarity and non-homeostatic flow rates [38]. Figure 11 is shown to clarify this statement. Multiple cut-planes are created to illustrate the velocity contours within the flow at the mentioned locations. At all three cross-sectional locations x_1, x_2 , and x_3 , the recirculation zone behaves slightly different in the non-Newtonian simulations, with the jetlike centerline flow being pushed slightly to the right.

The same effect is observed in Fig. 12, where a small separation region is formed close to the inlet in the Newtonian flow simulation of the second test subject vessel, which is nonexistent in the non-Newtonian counterparts. Moreover, the Newtonian simulation of this patient has a slightly stronger swirling motion close to the outlet region.

As mentioned before, from a clinical point of view, the WSS is the primary hemodynamic quantity of interest in this work. In the literature, the homeostatic range of WSS in the “human cephalic vein” is reported to be between 0.076 and 0.76 Pa [4,25,30,37,39]. In a parallel study [40], we substantiated these values for the cephalic vein in the present patient cohort via an integrated clinical, computational, and statistical investigation. In the same study, we found only a 3.2% difference in the length of the low-WSS ($\tau_w \leq 0.076$ Pa) and low-TAWSS (TAWSS ≤ 0.076 Pa) regions in 2D patient-specific simulations with and without pulsatility.

Formerly, we measured a 7% difference in the length of low WSS regions ($\tau_w \leq 0.076$ Pa) between Quemada and/or Casson and Newtonian CFD simulations of 2D patient-specific domains using a spectral elements analysis numerical scheme (NEK5000 Argonne National Laboratory) [41]. However, in a three-dimensional analysis using a 3D finite-element numerical scheme, this difference is less than 2%, which indicates that the non-Newtonian effects are even more insignificant in 3D simulations.⁵

In Fig. 13, the solid red zones represent the locations where the TAWSS at the end of the sixth cardiac cycle ($t/t_p = 1$) has dropped below the lower threshold (≤ 0.076 Pa) for subject 27. The Newtonian simulation shows a slightly larger region of low-WSS. We acknowledge that even this parameter exhibits small sensitivity to non-Newtonian effects. Instantaneous WSS follows the same trend for subject 12 (Fig. 14), where the Newtonian simulation shows less than 2 Pa (1%) larger instantaneous WSS values in the three locations indicated. Regardless of the shear stress thresholds, it is clear that the effects of the geometry on the hemodynamics are far more important than the non-Newtonian effects, which is in agreement with Refs. [42] and [43].

Although implementation of non-Newtonian models in CFD practice would be expected to require more computational effort to compute the variable viscosity, the opposite turns out to be the case. The dissipative non-Newtonian effects did modify the flow in such a way that it took fewer iterations per time step to converge as compared to a Newtonian simulation. Therefore, non-Newtonian simulations took comparable central processing unit time, despite the added computational cost for the non-Newtonian constitutive relations calculations. Marrero et al. [44] reported a similar finding in their article.

5 Summary and Conclusion

CFD simulations provide a noninvasive means to examine the hemodynamic stimuli that trigger the development of stenosis in renal failure patients with autogenous fistula access. However, the importance of implementing non-Newtonian viscosity relations in

⁵In Ref. [30], we also observed that non-Newtonian effects manifested in the frequency of shedding as well, resulting in appreciable differences between Newtonian and non-Newtonian hemodynamics when significant unsteadiness is present.

Fig. 13 Critical TAWSS for subject 27 at $t/t_p = 1$ of the sixth cycle. Red zones mark the locations where TAWSS has dropped below 0.076 Pa. Newtonian flow exhibits a slightly larger red zone.

CFD simulation for these patients with nonphysiological hemodynamics is yet to be determined.

At first, differences in blood viscosity for ESRD patients versus a normal population, namely lower values of whole blood viscosity and a wider Hct distribution, appeared to further amplify the need for a proper implementation of non-Newtonian constitutive relations. Also, it was noted that Hct should be accounted for as an independent variable in the constitutive model as each ESRD patient endures drastic variations of Hct levels on a time scale of months during the chronic treatment. Based on these observations, Quemada and Casson models were chosen to implement in this study. The CFD simulations were performed using patient-specific venograms, pulsatile waveforms, and viscosity data obtained from the patients’ blood samples.

We formerly reported 7% difference between Newtonian and non-Newtonian nonhomeostatic low-WSS (≤ 0.076 Pa) regions in ESRD patients’ venous flows using a different numerical scheme [30,45]. We were surprised to witness even less significant discrepancy when the investigation was extended to include pulsatility and three dimensionality (less than 2%). It is expected that the viscous dissipative effects are more pronounced in non-Newtonian flows. Hence, thicker viscous sublayers and flatter velocity profiles are expected in these flows as well as less

Fig. 14 Instantaneous WSS for subject 12 at $t/t_p = 0.5$. Newtonian flow shows a slightly higher instantaneous WSS at the locations indicated with arrows.

frequent occurrence of secondary flow zones [46]. This is particularly important in the context of sensitivity to particle residence time and stasis in these patients, i.e., Newtonian simulations may overpredict the severity of stasis in recirculation packets. For the WSS, the results indicate that the Newtonian simulation may also overpredict the vulnerability to neointimal hyperplasia and the onset of stenotic sites as it predicts slightly larger low-WSS zones (≤ 0.076 Pa). Ultimately, the combination of abnormally high dialysis-induced flow rates with the natural curvature of the cephalic vein increases the likelihood of a nonhomeostatic WSS distribution that exacerbates the intimal hyperplastic adaptive growth. Therefore, we suggest that the influences of the vessel geometry play a far more determinant role in patient-specific hemodynamics than the non-Newtonian effects.

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Nomenclature

D_{II} = second invariant of strain rate tensor
Hct = hematocrit

t_p = pulsation period time
 $\dot{\gamma}$ = shear rate
 μ = blood viscosity
 μ_F = plasma viscosity
 ρ = blood density
 τ = shear stress

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