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A Predictive Framework to Elucidate Venous Stenosis: CFD & Shape Optimization

S. M. Javid Mahmoudzadeh Akherat*,

Mechanical, Materials, and Aerospace Engineering Department, Illinois Institute of Technology, Chicago, IL, USA

Kevin Cassel,

Mechanical, Materials, and Aerospace Engineering Department, Illinois Institute of Technology, Chicago, IL, USA

Michael Boghosian,

Mechanical, Materials, and Aerospace Engineering Department, Illinois Institute of Technology, Chicago, IL, USA

Mary Hammes, and

Department of Medicine, University of Chicago, Chicago, IL, USA

Fredric Coe

Department of Medicine, University of Chicago, Chicago, IL, USA

Abstract

The surgical creation of vascular accesses for renal failure patients provides an abnormally high flow rate conduit in the patient's upper arm vasculature that facilitates the hemodialysis treatment. These vascular accesses, however, are very often associated with complications that lead to access failure and thrombotic incidents, mainly due to excessive neointimal hyperplasia (NH) and subsequently stenosis. Development of a framework to monitor and predict the evolution of the venous system post access creation can greatly contribute to maintaining access patency. Computational fluid dynamics (CFD) has been exploited to inspect the non-homeostatic wall shear stress (WSS) distribution that is speculated to trigger NH in the patient cohort under investigation. Thereafter, CFD in liaison with a gradient-free shape optimization method has been employed to analyze the deformation modes of the venous system enduring non-physiological hemodynamics. It is observed that the optimally evolved shapes and their corresponding hemodynamics strive to restore the homeostatic state of the venous system to a normal, pre-surgery condition. It is concluded that a CFD-shape optimization coupling that seeks to regulate the WSS back to a well-defined physiological WSS target range can accurately predict the mode of patient-specific access failure.

*Corresponding author: smahmou1@iit.edu (S. M. Javid Mahmoudzadeh Akherat).

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Keywords

CFD; Hemodynamics; Shape Optimization; Neointimal Hyperplasia; Vascular Access; Arteriovenous Fistula; Hemodialysis

1. Introduction: Neointimal Hyperplasia

A vascular access is necessary to provide adequate blood flow rate to perform hemodialysis on patients with end-stage renal disease (ESRD). The access that provides the best outcomes is the arteriovenous fistula (AVF), which is a direct surgical connection between the arterial and venous systems at an anastomosis. Unfortunately, the primary success rate for AVF remains at best 23%^[1]. There are two locations for AVF that lead to different outcomes. The first recommended AVF with the best outcomes is a radiocephalic fistula (RCF), which is placed in the lower arm. These often fail, especially in elderly and diabetic patients, owing to a juxta-anastomosis venous stenosis^[2]. Increasingly, therefore, more AVF are being placed in the upper arm, known as the brachiocephalic fistula (BCF). BCF are created by surgically connecting the brachial artery to the cephalic vein near the elbow. The most common mode of failure in the BCF is cephalic arch stenosis (CAS), which occurs well downstream of the anastomosis in the curved portion of the cephalic vein near its junction with the axillary vein^[2](see Figure 1).

The creation of the BCF produces an anatomically and physiologically abnormal situation that leads to extreme non-homeostatic hemodynamics. High volume flow is diverted from a thick-walled, muscular, pulsatile artery into a thin-walled vein. Mean flow in the brachial artery increases from 56.2 ± 20.0 mL/min before creation of the BCF to 365.0 ± 129.3 mL/min one day after and to 720.4 ± 132.8 mL/min 28 days after creation^[3]. Comparison of hemodynamic changes over time shows that BCF have an increase in cross-sectional area and a dramatic increase in blood flow (mean $1,983 \pm 1,199$ mL/min) when compared to the RCF accesses (mean 870 ± 322 mL/min)^[4]. The extremely high flow rate in BCF causes an insult to the homeostatic state of the vascular system that leads to complications, including aneurisms, and contribute to venous stenosis and heart failure^[5,6].

This radical increase in the blood flow through a curved vein, such as the cephalic arch or at the anastomosis, disturbs the flow and leads to local regions of low wall shear stress (WSS). Low WSS has adverse effects on endothelial cells, including increased cell turnover, oxidative stress, and triggers a series of inflammatory genes that create neointimal hyperplasia (NH)^[7,8]. NH is a process that leads to formation of a thickened arterial/venous intimal layer followed by occlusion of the vessel (see, for instance, figure 1b). It is a common condition that often follows post-surgery trauma, stenting, angioplasty, changes of WSS or similar insults to the venous homeostasis, as a result of which the thickening of the vessel wall and continuous (sometimes ever-changing) wall deformation and hemodynamic-driven adaptation occurs. Aggressive NH will eventually lead to venous stenosis, causing access dysfunction requiring interventional procedures, such as angioplasty or stent placement, to maintain access patency. Additional triggers to the development of abnormal NH are injury to the endothelium owing to mechanical trauma from surgery or cannulation.

Nonetheless, the end result of NH is access failure that contributes significantly to the morbidity, mortality, and cost of providing hemodialysis to ESRD patients^[9].

Collectively, Taylor and Humphrey^[24], and others^[59,69] mentioned that mechanical loading on the blood vessel's wall can induce changes in gene expression associated with sub-cellular activity, triggering signals in cell culture that initiate proliferation, migration, differentiation, synthesis, apoptosis/cell suicide, etc. that when superimposed, carry the tasks of adaptation and development during maturity and maladaptation during vascular disease progression. In the words of the authors^[24]:

“Overall wall thickness tends to be regulated so as to maintain the circumferential wall stress near a target value, hence motivating the study of wall mechanics whereas smooth muscle is primarily responsible for synthesizing matrix proteins during development, it endows the mature vessel with its ability to constrict or dilate and thereby regulate blood flow locally.”

–C. A. Taylor and J. D. Humphrey

Given the above explanation on activation of growth factors due to mechanical loads, it becomes clear that understanding the mechanisms behind NH is imperative as it has been reported to complicate 30% to 50% of vein grafts, vascular accesses, and angioplasty procedures^[32]. In the current clinical-computational investigation, almost 90% of the human subjects who received BCF for dialysis experienced CAS and access failure thus far (33 subjects out of 37 within three years). Angioplasty, endarterectomy, and other endovascular surgeries performed to resurrect the access patency have also been reported to fail due to post surgical restenose in 30% to 50% of the operations within the first year^[39].

Even though it is hypothesized that NH is a response to abnormal or injurious conditions in the cardiovascular system, it is unclear if this adaptive response is a normal physiological response or whether it is an abnormal pathophysiological one^[32]. The reader is suggested to consult^[23,24,27,32,35,37,48,49,56] for further details on hyperplastic intimal thickening¹. It is also worth mentioning that NH is categorized into Hyperacute, Acute, and Chronic, which occur on time scales of multiple hours, weeks, or months, respectively^[39]. The type of NH lesion detected in our patients cohort is primarily chronic, with a distribution patterns that might diffuse throughout large portions of the vessel or can be focal to the anastomosis or specific regions. For example, Figure 1b depicts a distributed-type NH in one of our patients.

While the processes that regulate NH development remain under investigation on a molecular level, it is known that NH is a summation of complex cellular proliferative, migrative, and extra-cellular matrix (ECM) deposition activity. The proliferation/migration of smooth muscle cells (SMC) is thought to require a phenotypic modulation^[35,32]. Post injury WSS changes endow the SMC in the media with the ability to gain the mobility to migrate from the media into the intima, where they proliferate and synthesize contractile

¹Other triggering pathophysiological factors of NH growth are: 1) injury, e.g. owing to mechanical trauma at the time of surgery (VA creation surgery for stenosis and angioplasty/stenting surgery for restenosis, all can causes damage to endothelia. The damage to the tissue can go as deep as SMC at which point the media gets exposed to the blood stream) or the dialysis needles or the denudation of the endothelium ($\tau_w \sim 30$ Pa), and 2) hemodynamically exerted abnormal wall shear stresses.

proteins (synthetic phenotype). These are, in fact, the active type of smooth muscle that are observed in the histology observation of progressed NH lesions^[32,35,36,37,38,39,60,70,71].

The conventional continuum mechanics analysis of the soft tissue growth, growth and remodeling (G&R), is a first principles approach that could be used to model the biomechanical mechanisms underlying NH^[23,59,27,29,57]. However, the constitutive relations of production, removal, and turnover of the wall constituents that would define the exact functional behavior of this growth are yet to be identified as the etiology of the NH and intercellular cycle of events that lead to its progression are still unknown. In particular, human histological data, specifically for renal failure patient's venous NH, is extremely rare and unreliable. This lack of biological information is an impediment to the development of the first-principles constitutive relations that define the stress-mediated growth of NH².

In light of this articulation, in the ensuing sections we will introduce our novel computational method that elucidates the adaptive venous wall thickening that carries the task of restoring wall stresses back to a target value and locally regulating system's flow rate in chronic dialysis patients.

2. A Shape Optimization Model of Neointimal Hyperplasia

In lieu of the detailed information required to carry out a first-principles G&R simulation, shape optimization holds the promise of directly linking the local hemodynamic conditions to the concomitant shape changes via NH. Arterial and venous adaptations serve to restore vessel WSS to homeostatic norms^[53,54]. The migration and proliferation of SMC is simply the basal mechanism for shape evolution that is, broadly speaking, a physiological effort to manipulate WSS so as to maintain wall stresses near a target value. In a parallel study, we have statistically and computationally identified a physiologic range of WSS in the cephalic vein pre-surgery. This range was determined to be $0.076 \leq \tau_w \leq 0.76$ Pa^[61], which is consistent with the range given in previous literature^[22].

The framework proposed in this article consists of a combination of shape optimization and CFD to circumvent the unknown rates and amounts of constituents turnover, production, and removal that occur in concert to create the hyper-plastic lesion in the tunica media. The argument here is that the shape evolves through the NH mechanism to readjust wall thickness, such that the resultant flow and consequent WSS exertion on the walls relaxes back to the normal physiological range. This shape evolution can be simulated numerically through a mathematical shape optimization by extremizing a physiologically meaningful objective functional. Similar attempts in pre-surgical planning and endovascular device design have been performed by Marsden et. al.^[44], W. Yang et. al.^[43], Abraham et. al.^[46], Dur et. al.^[45].

The vessel deformation, whether a favorable adaptation that preserves the lumen or an unfavorable stenotic lesion that decreases the luminal area, is the natural response to an insult to a stable homeostatic state of the vasculature. In the case of ESRD patients with

²Dr. Alan Dardik, Yale University, personal communication, October 6th, 2015.

autogenous AVF access, the insult is the dramatic increase in the blood flow rate after introducing the arterial flow into the vein that brings about the consequent violent hemodynamics. The adaptive response manifests in the form of NH and the eventual stenotic growth.

2.1. Patient-Specific Hemodynamic Simulations

The ESRD patients in this study developed maturity of vascular access 8–32 weeks post fistula surgery. Maturity is reached when the vein is able to be used for hemodialysis with two needles, thereby defining the time of maturation (TM). Thereafter, the superficial vein can be accessed with dialysis needles to facilitate the high blood flow rate needed for hemodialysis. TM is thus the starting point of the chronic dialysis treatment. Patient-specific geometry and hemodynamic information (X-Ray venography images, Doppler velocity measurement, whole blood viscosity (WBV), hematocrit levels, etc.) are our model inputs.

At the TM (8 – 32 weeks), a CFD simulation is carried out using the available clinical data by implementing the commercial finite element code COMSOL Multiphysics. Boundary conditions for these simulations are patient-specific parabolic velocity profiles prescribed at the inlet, no-slip condition on the upper and lower rigid impermeable walls, and a coupled zero–pressure, zero–divergence enforced at the outlet of the domain. Classical momentum and mass conservation equations are solved for this problem using a Galerkin-Petrov projection method in a multi-frontal massively parallel sparse (MUMPS) direct steady solver. The flow is assumed to be Newtonian. Pulsatility and non-Newtonian effects were both attended to previously and were found to be insignificant in our patient cohort^[61,62,63,64,77,75,76]. WBV for the CFD simulation is taken to be the patient-specific high-shear rate asymptotic viscosity values from the viscometry tests^[62,78].

A laminar inflow boundary condition for the inlet was considered to introduce a fully-developed velocity profile into the domain³. For the inlet velocity condition, the parabolic velocity profile is:

$$u = - \left(\frac{U_{max}}{R^2} \right) (R^2 - y^2), \quad v=0, \quad w=0, \quad (1)$$

in which U_{max} is the maximum venous blood flow velocity reported by the interventional radiologist from Doppler velocimetry (Figure 2-b) of the specific patient under observation^[63]. For patient number 12 at TM, for instance, $U_{max}=0.54333 \left[\frac{m}{s} \right]$. R is the patient-specific vessel radius measured from the protocol venograms (Figure 2-a). The unsteady, incompressible, Newtonian Navier-Stokes equations are:

$$\rho (\partial_t \mathbf{u} + \mathbf{u} \cdot \nabla \mathbf{u}) = -\nabla p + \nabla \cdot (\mu (\nabla \mathbf{u})) + \rho \mathbf{f}, \quad (2)$$

³We could have alternatively introduced patient-specific cardiac waves and performed the time-averaging to obtain time-averaged WSS distribution.

$$\nabla \cdot \mathbf{u} = 0, \quad (3)$$

which enforce momentum and mass conservation, respectively, where $\mathbf{u}$ is the velocity vector. No body force $\mathbf{f}$ exists in the fluid domain, and μ is the patient-specific WBV. This value for subject 12 is $\mu = 0.00328$ [Pa.s]. In all simulations, density is always taken to be a constant value of $\rho = 1050$ $\left[\frac{kg}{m^3}\right]$.

Having the CFD simulation completed at TM, we will have identified: 1) the patient-specific inlet venous pressure that would create such flow rate and 2) the patient-specific WSS distribution at TM that triggers the adaptation processes. Once the fixed patient-specific pressure at the inlet is obtained, it serves as the new pressure Dirichlet boundary condition at the inlet for the shape optimization. The prescribed pressure for patient number 12 is $p = 160$ [Pa], for example. It is hypothesized that regions where WSS drops below the lower threshold, $\tau_w = 0.076$ Pa, are the most susceptible to the onset of NH. These regions are illustrated with a thick red line in Figure 3. One would naturally expect to see these locations in the curved portion of the domain with a high flow rate, where flow could separate and reattach to the walls (multiple times in some instances, depending on the complexity of the geometry, the Reynolds number, and inlet velocity).

2.2. Hypothesis: The CFD-Shape Optimization Coupling

At this stage, we utilize COMSOL Multiphysics' optimization module to demonstrate that, in fact, through shape optimization computations, we can predict the shape that the vessel will ultimately evolve toward. If our hypothesis holds, this evolved shape best regulates the manipulated WSS distribution back to a favorable range with the hemodynamic conditions closest to the homeostatic state of the vasculature. In other words, we postulate that the evolution of the shape of the vessel is governed by first-principles optimization definitions. Obviously, the body naturally attains this goal by changing the balance between the constituents amounts, turnovers, and production-removal rates in these locations. However, our optimization point-of-view bypasses the first-principles biological/cellular analysis and is only concerned with the resulting shape.

From the optimization standpoint, the mathematical problem reads:

$$\text{Minimize } J, \quad (4)$$

where the objective functional J is defined as

$$J = \int |\tau_{w|Actual}(\mathbf{q}) - \tau_{w|Homeostatic, Mean}| dx, \quad (5)$$

subject to the constraints that the Navier-Stokes equations (2) and (3), i.e. the equilibrium, along with their associated fixed pressure Dirichlet boundary conditions, are satisfied. In

equation (5), $\tau_{w/Actual}(\mathbf{q})$ depends on the numerical solution of the Navier-Stokes equations obtained from the patient-specific CFD simulation at TM, and $\tau_{w/Homeostatic,Mean}$ is the desirable physiological WSS distribution sought by virtue of the homeostatic definition of the target WSS value in the cephalic vein, which is taken to be equal to 0.418 [Pa]. This is the mean value within the mentioned physiological range. $\mathbf{q}$ is a vector quantity of parameters that controls the geometrical deformations of interest. For a two-dimensional domain, WSS is $\tau_w = \mu \left(\frac{\partial u}{\partial y} + \frac{\partial v}{\partial x} \right)$. Through this optimization process, the vessel reshapes itself in such a way that it can sustain the WSS in the neighborhood of a physiologically acceptable effective value. It needs to be reiterated that the geometric and hemodynamic conditions at TM are used as the starting basis for the proposed shape optimization procedure.

Parametrization of the vessel shape has to be done in such manner as to provide sufficient optimization variables and topographical accuracy in order to achieve an acceptable extrema while maintaining a reasonable computational cost. To this aim, four different parametrization schemes were explored, as presented in Table 1. For all parametrization schemes, q_i will be taken as the optimization variables, and d_i are the scale factors. For the NURBS definition^[65,66,67], $P_i = (x_{i1}, x_{i2})$ are the coordinates of the control points $i = 0, \dots, n$, w_i are the corresponding weights, and $B_{i,p}$ is the degree p B-spline. Similarly, $b_{i,n}$ is a degree n Bernstein curve. For all parametrization techniques, the edge variable s ranges from 0 to 1 along the wall.

Obtainment of the gradients of the functional with respect to the control variables is a computationally challenging CFD problem as using adjoint solutions is numerically expensive and noisy. There are, however, notable contributions of Abraham et. al.^[46] and Quarteroni et. al.^[47] who used gradient-based methods for shape optimization in idealized two-dimensional and/or steady blood flow problems. We agree with Marsden et. al.^[44] that intrinsically complex geometries, unstructured grids, and time dependence in blood flow problems poses formidable challenges in implementation of gradient-based optimizers. Naturally, we implemented the derivative-free optimization methods that were available in COMSOL Multiphysics.

Bound optimization by quadratic approximation (BOBYQA), a gradient-free method developed by Powell^[42], is particularly of interest in the conduct of this research due to its robust convergence properties. At each iteration of the optimization algorithm, the deformations are achieved according to one of the parametrization schemes given in Table 1, and the re-meshing is done automatically by solving the Poisson equation to reach the smoothest distribution of a numerical grid in the deformed domain^[34]. Once the newly generated mesh is obtained, the CFD module runs again to find the new distribution of the WSS on the walls that will feed the objective functional again to evaluate the improvement of the result. The flow chart for this technique is illustrated in Figure 4. The optimality criteria is set to be 0.001 for minimization of the objective functional defined in equation (4). The number of cost functional evaluations is directly dependent on the optimality tolerance definition and grid size chosen for the CFD module and is directly affected by the choice of constraints. In this work, the number of cost functional evaluations for multiple cases studied

here ranged from 1,000 to 10,000, depending on the complexity of the geometry and hemodynamics. The total number of degrees of freedom required for sufficiently spatially resolved two-dimensional domains obtained from grid-independence studies ranged from 100,000 to 200,000 on a subject-specific basis depending on the geometry complexity and the Reynolds number, where second-order accurate discretization for first and second-order derivatives spatially and temporally were implemented.

3. Results

3.1. Shape Parametrization Validation

The best method of parameterization would change the geometry in order to achieve the closest distribution of WSS to the physiological value imposed by the objective functional. Therefore, the method that enhances the WSS distribution marks the most promising for patient-specific shape optimization. NURBS inherently form a sophisticated basis function for parametrizing complex geometries. However, they tend to become numerically noisy as the number of control variables increase. In the two-dimensional geometries considered herein, the geometric reconstructions consist of 100 control points on each of the upper and lower walls of the domain. Each point has three corresponding control variables (x , y , $weight$), totaling 600 control variables for the whole domain. The computational cost and the numerical instability brought about with this number of optimization variables virtually make implementation of NURBS impossible even for the two-dimensional domains considered.

Having eliminated implementation of NURBS, Table 2 and Figure 5 summarize the results achieved from different basis functions used as the parametrization method. Truncated Fourier Sines (Figure 5a) hypothetically can approximate any given shape with an infinite number of terms. However, because the number of independent variables for optimization is limited, they exhibit an unavoidable bulging effect due to their natural sinusoidal shape that do not correspond to anatomically meaningful cardiovascular geometries. Moreover, the very large number of truncated sine terms required to potentially represent a complex patient-specific venous geometrical shape poses yet another pragmatic limitation (20 terms were used here).

In order to at least avoid the bulging effect of Fourier sines, modified truncated Fourier sines were introduced (Figure 5b). They only allow inward growth of the geometry to better represent a stenotic lesion. In this scenario, an axial cut-off location was also defined that limits the deformation to the natural arch section of the vein. Although this method shows a significant drop in the objective functional, it is heavily reliant on user discretion as to where to define the cut-off location between the fixed and the deformable sub-domains. Moreover, only four optimization variables were practical to solve this problem, which do not represent a mathematically well-posed problem. In addition, they only provide a conic cone shape that very crudely represents a stenotic shape. The Hicks-Henne bump function, while more sophisticated than the modified truncated Fourier sines, also rely on a cut-off location with four independent variables (Figure 5c). In the Hicks-Henne bump function, the first parameter, q_1 , determines the bump's maximum location, while q_2 determines the width of the bump.

Finally, Bernstein basis functions were found to provide the best balance between computational efficiency and geometric flexibility. In particular, optimization results for different degrees of Bernstein basis functions were evaluated to determine its effect on the evolution of the shape optimization. The results for degree 10, 20, and 30 polynomials were compared, and it was determined that because all three lead to essentially the same optimized shape and value of the objective functional, 10th degree basis functions with 20 optimization parameters have been used throughout to minimize the computational cost (see Figure 5d).

3.2. Hypothesis Verification

Using different parametrization schemes, the vessel geometry has become narrower in an attempt to bring the manipulated, dialysis-induced WSS distribution back to a homeostatic range. In other words, through the inward growth of the wall, by the virtue of signal transduction that triggers SMC migration and proliferation and the subsequent accumulated NH, the luminal shape of the vessel is optimized to readjust the WSS back to the target physiological range. See Figure 6, where the thickening of the wall resulted from the CFD-shape optimization simulations is demonstrated.

Figure 7 is generated to visualize the difference between the homeostatic WSS distribution ($0.076 \text{ Pa} \leq \tau_w \leq 0.76 \text{ Pa}$) in a two-dimensional domain at TM (7a), at predicted failure mode (7b), and at actual patient-specific failure that occurred 12 months post operative (7c). An evident restoration of the homeostatic WSS in the adaptively evolved shape is discernible. In fact, at TM, the locations with in-range WSS in the two-dimensional domain constitute 38% of the entire wall length. This number after adaptation in the actual patient-specific case at the time of failure increases to 53%, which is indicative of the body's partial success in restoring homeostatic WSS in some regions of the vein's lumen (the same was reported by McGah et. al.^[79]). Our model predicts an increase to 63%, which agrees acceptably with the patient-specific data. The restoration of WSS back to the physiological range as well as the regulation of the high and low WSS values can be better perceived from Figure 8, where WSS [Pa] is plotted versus x location [m] for the upper and lower walls on the patient-specific geometries at TM and predicted failure.

One very important physiological factor driving the adaptation process in the venous system is the overall network pressure impedance. In this study, patient-specific inlet pressures are fixed at the inlet and a zero pressure Dirichlet boundary condition along with a zero-traction are applied at the outlet. While the geometry becomes narrower close to the outlet region in the arch section, a pressure buildup manifests within the domain upstream of the arch. As a result, the flow rate will drop in order to maintain the same pressure difference imposed on the domain. In medical terms, this pressure buildup can be interpreted as hypertensive transmural pressure, i.e. cyclic stresses, on the vessel walls that happens to be endemically detected in the ESRD patients under chronic dialysis (see Figure 9). We suggest that transmural pressure may be a secondary effect in vasculature adaptation, while WSS remains the primary triggering factor. The drop in flow rate is also another common condition in ESRD patients that signals the access failure in clinical practice, at which point invasive operations such as stenting and angioplasty are exploited to resurrect the native access. For

instance, the test case at hand had a patient-specific inlet velocity of 0.54333 [m/s] at TM. However, after the optimal shape was obtained, this value dropped to 0.18 [m/s]. The latter value is comparable to the same value that all of our patients exhibit as the inlet velocity at the time of mapping, right before the access surgery when the fistula is not yet surgically created and the venous environment is still in normal homeostasis. Dilation in the vessel used for dialysis access can also be elucidated via this hypertensive pressure build up, which is another venous adaptive response in ESRD patients that occurs in the straight segment of the blood vessel.

In fact, the most effective means of verifying the proposed hypothesis might arise from direct comparison of diameter variations along the flow direction through time. In Figure 10, diameter changes from TM to the actual failure is compared to the diameter changes from TM to the predicted failure. ΔD in Figure 10 is defined as:

$$\Delta D = [D_{|Failure} - D_{|TM}] - D_{|Correction}, \quad (6)$$

where $D_{|Failure}$ is either the local diameter at the actual failure or the computationally predicted failure, $D_{|TM}$ is the local diameter at time of maturation (the same for both actual and predicted scenarios), and $D_{|Correction}$ is either the difference between the overall average diameters at TM and the predicted or the actual failure. The correction diameter has been applied to the calculation to exclude the “*global*” dilation effect that is prevalently seen in the fistula environment and is outside the scope of the present work⁴.

The aforementioned dilative effect can be seen in the straight section of the vein upstream of the arch in Figure 10, where ΔD from TM to failure in both predicted and actual scenarios acquires positive values. The reader is recommended to take particular note of the negative

ΔD values in the arch section of the vein arising from “stress-mediated stenotic (neointimal hyperplastic) growth” and the positive ΔD values in the straight segment of the vein arising from “pressure-mediated dilative growth”. From the time of anastomosis surgery until maturation, when dialysis begins, the cephalic vein experiences an overall growth in diameter by approximately a factor of two. This is a result of the pressure-mediated dilative growth that the vein experiences during arterialization. This process continues post maturation, but at a slower rate. Presumably, this would have also occurred in the arch section; however, the WSS-mediated neointimal hyperplastic growth owing to the curvature of the vein dominates in this region, resulting in a net inward constriction ultimately leading to stenosis.

The same analysis was performed for multiple other randomly selected subjects who developed CAS in our patient cohort. The results exhibit the same findings for WSS restoration and evolution of vessel shape in the form of excessive NH that match very closely with patient-specific images and data at the time of failure (see Figures 11 to 15). Note particularly that in some cases the stenosis is centered in the elbow of the arch, i.e. in

⁴This effect is called maturation or the arterialization of the access post introduction of arterial pressure into the venous system. Failure to mature is another condition that deserves its own separate investigation

the region of the maximum curvature, while in other cases the stenosis occurs in the arch closer to its junction with the axillary vein at the outlet of the domain. In both instances, the predicted shape captures this accuracy. The hemodynamic information for these patients can be found in Table 3.

Additionally, we revisited the choice of the target value in the objective functional defined in equation (5). Although the target value we used is the mean value of the specified physiological range of WSS in the cephalic vein, other target values from this range resulted in the same occluded vessel shape as all these WSS target values result in a homeostatic state of the vessel. See Figure 16, in which various target values were implemented in the CFD-shape optimization coupling where the maximum D value obtained from different target values in the range mentioned remained identical.

4. Three-Dimensionality, Bifurcations, & Temporal Aspects

4.1. Patient-Specific Three-Dimensional Shape Optimization

While performing patient-specific three-dimensional shape optimization coupled with CFD with millions of numerical degrees of freedom and tens of control variables might seem numerically daunting, particularly for regular medical practice, we here present a first principles engineering method to overcome this obstacle. As a proof of concept, a patient-specific three-dimensional computer aided design (CAD) model was made from lofting multiple cross sections that represent the local diameters of the vein for subject number 12 shown in Figure 17 (similar to^[63,72,73,74]). These local diameters form the basis of the optimization parametrization as they are used directly as the control variables. This way, the luminal surface does not need to be parametrized with 10th or higher degree Bernstein basis functions and therefore, while three-dimensionality poses increased computational cost, the optimization is done more efficiently without jeopardizing the accuracy of the shape evolution. The same fully-developed inlet condition as the two-dimensional case and the same outlet, walls, and viscosity imposition are considered in the three-dimensional domain that consists of 1M volume tetrahedral elements. For patient 12, the subject-specific Reynolds number with the constant reference viscosity of 0.0035 [Pa.s] would be $Re = 600$, which is well below the Poiseuille flow instability and turbulence threshold and hence no turbulence modeling is required. Moreover, the simulations discussed thus far are all stationary and therefore, it stands to reason that no turbulent scales are present. We reiterate that the inlet pressure is time-independent^[61,63]. The alternative would be to consider patient-specific cardiac waveforms and, instead, consider the TAWSS distribution in the domain, which is computationally very costly. In this specific application, as we showed before^[61,62,63], the WSS distribution is found to be insensitive to pulsatility and implementation of the non-Newtonian constitutive relations^[61].

The local diameters are allowed to change as the optimizer evaluates the objective functional discussed in equation (4). As illustrated in Figures 17 and 18, the resulting geometry is constricted in the same portion of the arch region as for the actual veins, and a WSS distribution closer to the homeostatic one is obtained in both predicted and actual cases, while the flow rate drops and transmural pressure upstream of the arch increases as before. As can be seen from Figure 18, the optimal shape has a better in-range WSS distribution

compared to TM that is similar to the actual patient-specific values at the time of failure. Notice, in the patient-specific failure case, that the adaptive response has partially restored the homeostatic WSS by the time of failure.

4.2. Patient-Specific Bifurcated Venous Branches

On rare occasions, there are patients who are reported to have bifurcated cephalic vein geometries. Subject 119 in our study (Figure 19) exemplifies one of the bifurcated venous geometries. Patients with bifurcated cephalic veins also may receive BCF as the dialysis access method and, therefore, could potentially experience access failure due to excessive NH growth. Clinically, subject 119 also exhibited access failure due to NH. The same method of parametrization and shape optimization coupled with CFD has been exploited to check the applicability of the proposed method to bifurcated venous branches. The results indicates the same finding as for the non-bifurcated venous geometries discussed earlier. The occlusion develops focally in the bifurcation area, where hemodynamics are more complex and alteration in WSS and other hemodynamic parameters are expected to trigger the adaptive cellular responses. Moreover, as in arterial bifurcation, the bifurcation zone is a strategic vantage point, controlling the flow field, flow rate, and all the consequent hemodynamics downstream in the succeeding branches. Development of excessive NH and stenosis in this location will mitigate flow violations downstream and will globally remodulate the WSS and transmural pressures exerted on the branch. Topographically, the predicted results and the patient-specific data for 119 matches closely as inferred from Figures 19 to 21. The proposed framework predicts an occlusion immediately upstream of the bifurcation zone, similar to the patient-specific failure occlusion 24 months post operation. Bifurcated veins, as expected, are computationally more demanding for shape optimization coupled with CFD analyses. In some scenarios, the occlusions in the bifurcation zone can become so severe that hydrodynamic instability creates vortex shedding in the numerical domain that causes convergence difficulties⁵.

4.3. Temporal Considerations

Although the shape optimization methodology predicts the failure modal shape, it does not address the time required to evolve toward this shape. This information must be discerned from the clinical data. Post-processing assessment of the numerical results in liaison with diameter variations through time on a patient-specific basis was performed to identify correlative time-dependent relations.

Recall that the ESRD NH growth is a chronic condition and occurs on time scales of months in our patients. From the 37 patients who completed our study, 4 finished without any evident clinical failure within 36 months, 2 developed CAS at 36 months, 10 developed CAS at 24 months, 14 developed CAS at 12 months, and 7 developed CAS at 3 months post fistula surgery. See Figure 22 for the normal distribution of CAS failure probability and frequency in our patient cohort.

⁵We detected flow instability and vortex shedding in some cases with severe constrictions predicted by shape optimization at the bifurcation zone, for which we implemented time averaged WSS (TAWSS) for the shape optimization objective functional at much higher computational costs. Such findings will be reported in future publications.

It is important to note that NH is a condition that affects only the intimal thickness of the vessel. Therefore, the assumption here is that medial and adventitial thicknesses are constant while the overall mass and cross-sectional area of the system is increasing due to the proliferative activity. The same D description discussed in equation (6) was calculated for the 33 patient and then averaged over their respective time of failure (either 3, 12, 24, or 36 months)⁶. Acquiring the data as such, we suggest that the thickening of the cephalic vein's medial layer in our patient cohort has occurred on a daily rate of $4.6 \pm 2.5 [\mu m]$. For instance, for subject 12 whose hemodynamic information was discussed herein, the average D from TM to predicted failure is 0.002166 [m], which translates to a time to failure of 471 days (15.7 months) according to the rate we propose. Actual patient-specific failure for this patient was recorded at 12 months post surgery. We reiterate that this is a rough and purely statistical estimation of the temporal dependence in the proposed predictive method. While more precise data acquisition techniques on larger cohorts with denser follow-up sessions would result in more accurate occlusion rates, variational data assimilation and system identification may also assist this aim.

As mentioned before, four subjects completed the 36 month study without experiencing failure. This success in dialysis treatment is not explicable by the method we have introduced. Nevertheless, two descriptive possibilities exist to elucidate the successful access patency for these four patients in the time-span of our study: 1) from a pathobiological stand point, this suggests the presence of an intercellular-pathophysiologic mechanism that inhibits signal transductions and the production of vasoconstrictors which would provide this favorable failure resistance. 2) The more probable scenario is, while it is possible that these four patients have an inherent physiological resistance to NH and CAS, it may still simply be the case that the onset of CAS has been delayed beyond three years and it might occur in a time-span larger than the one this study was based on. The study of these sub-cellular phenomena is outside of the scope of the presented work but holds the promise of the invention of new methods that would provide failure-resistant dialysis accesses.

5. Conclusions

In our prospective study, 33 out of 37 ESRD patients receiving BCF access for chronic dialysis treatment experienced failure of their accesses due to excessive NH growth and a subsequent CAS within three years, at which point costly and painful interventional procedures were executed to revitalize the access. Therefore, obtaining a thorough understanding of the underlying mechanisms of CAS and access failure is imperative.

The primary intersection between hemodynamics and cardiovascular vessel shape change are vessel wall stresses. As a first foray, the homeostatic range of WSS in the cephalic vein downstream of the BCF anastomotic site has been obtained numerically for patient-specific conditions (0.076 to 0.76 Pascals). These values, however, are strongly violated by the arterial flow that is introduced in the vein post access surgery and maturation of the fistula. An adaptive response is then triggered which, after a series of hemodynamics-driven

⁶We disregarded the four successful accesses for the temporal analysis we performed, as we suspect that these four accesses may fail in a time-span larger than the one this study was performed on.

complex sub-cellular events, results in a dilative growth in the straight segment of the vein and a stenotic growth in the arch section.

Growth and remodeling, as a first principles continuum mechanics method, provides a rigorous means to simulate this effect in the soft tissue. Lack of in-depth understanding of signal transduction followed by phenotypical modulations that trigger the proliferative stress-mediated growth, however, is an impediment to the application of growth and remodeling to simulate venous neointimal hyperplastic deformations. In the absence of such knowledge, we have hypothesized that the venous geometric evolution through NH, instead, can be captured as a shape optimization evolution to restore homeostatic WSS and flow rate in the access environment. This can be computationally modeled using a strong coupling of CFD and shape optimization in two-dimensional and three-dimensional numerical domains. This method is not a substitute for a conventional G&R, but rather a compliment that is computationally less demanding and potentially more amenable to application in medical environments as it is reliant on available data in clinical settings. Therefore, because the two approaches are highly complementary, we believe that both should be pursued as G&R addresses the primary disadvantage of the method we proposed, i.e. CFD-shape optimization coupling does not include the rate at which the adaptation occurs and, consequently, the predicted time to stenosis.

The coupled CFD and shape optimization framework is found to be very effective in predicting the inward growth of the wall and the luminal diameter reduction within the cephalic arch of ESRD patients. Of those patients who exhibited CAS, our framework predicts stenosis in the arch at locations that are in very good agreement with patient-specific clinical data. This is found to be the case for typical cephalic arch geometries as well as less common, but computationally more challenging, bifurcated cases.

In addition, one three-dimensional case has been considered to show that the approach can be extended if three-dimensional imaging is available, such as via intravascular ultrasound (IVUS) or magnetic resonance angiography (MRA). In particular, patient-specific CFD-coupled-shape optimization has been performed on a simplified three-dimensional patient-specific geometry. The results are highly consistent with that of the two-dimensional cases.

Because no mechanical wall properties or biochemical growth mechanisms are required in this method, arterial and venous flows could be treated the same using this framework. Therefore, the study of NH and stenosis in an ESRD cohort will benefit the medical and biomedical community with stenosis and restenosis forecasting knowledge in both venous and arterial systems. One simply needs to impose the proper objective functional and constraints on wall stresses (either transmural pressure or shear stress). Therefore, the applications of this method can be extended to other cardiovascular conditions with hyperplastic growth origins, and the ones in curved or bifurcated regions e.g. carotid artery bifurcation disease, vasculitis, etc.

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(a)

(b)

Figure 1.

(a) An example of a protocol venogram showing the cephalic vein for subject 128 at time of maturation post surgery. (b) An evident stenosis and excessive NH developed at the time of failure in the cephalic arch of subject 128, 24 months later. The blood flow is from right to left.

(a)

(b)

(c)

(d)

Figure 2.

Subject 12 at TM: (a) protocol venogram, (b) the reconstructed two-dimensional CAD geometry, and (c) the Doppler measurement that is performed by the interventional radiologist. The blood flow is from right to left. Patient-specific WBV information (d) is obtained from a viscometry test [62].

Figure 3.

Streamfunction plots superimposed on WSS distribution at TM for subject number 12. Thick red lines in (a) illustrate the locations where the WSS drops below the lower threshold value (0.076 [Pa]), while thick green lines in (b) show the locations where the WSS is higher than the upper threshold value of 0.76 [Pa]. Both of these regions are outside of the physiologic WSS distribution range and hence, will trigger adaptive responses.

Figure 4.
Shape optimization coupled with CFD flow chart.

Figure 5.

Shape optimization performed for subject number 12 using: (a) Truncated Fourier Sines parametrization, (b) Modified Fourier Sines, (c) Hicks-Henne Bump Functions, and (d) Bernstein Basis Functions. The black frame illustrates the initial shape at TM where the optimization started from and the pseudo-color velocity magnitude contours (m/s) show the evolved shape.

Figure 6.

Initial patient-specific shape at TM superimposed on the predicted optimal shape. The red-zone depicts the excessive NH growth for subject 12 that results in a new luminal shape that better regulates the WSS distribution. This red-zone represents the newly generated SMC-tissue that has reduced the luminal diameter.

Figure 7.

The distribution of in-range WSS [Pa] for subject 12 at (a) TM, at (b) failure predicted by CFD coupled with shape optimization, and (c) at actual patient-specific time of failure. The physiological distribution range of WSS in the cephalic vein is 0.076 Pa τ_w 0.76 Pa shown here by thick-blue lines. The optimal shape has a better in-range distribution compared to TM, and so does the actual patient-specific shape at the time of failure. Blue: 0.076 Pa τ_w 0.76 Pa, Red: τ_w 0.076 Pa, Green: τ_w 0.76 Pa.

Figure 8.

WSS [Pa] versus x location [m] of the blood vessel on the upper and lower walls of patient-specific geometries for subject 12 at TM, at actual failure, and at predicted failure. Notice the regulated WSS [Pa] distribution upstream of the arch ($-0.07[m] \leq x \leq 0$) and within the arch ($-0.12[m] \leq x \leq -0.07[m]$) at predicted failure compared to the WSS distribution at TM. Dashed-black line: upper wall at TM, dashed-red line: lower wall at TM, black-dotted with plus sign: upper wall at actual failure, red-dotted with plus sign: lower wall at actual failure, solid-blue line: upper wall at predicted failure, and solid-green line: lower wall at predicted failure. The blood flow is from right to left.

Figure 9.

Transmural pressure [Pa] at (a) TM, (b) predicted failure, and (c) actual patient-specific failure mode. A pressure buildup causes hypertension within the venous system used for dialysis access, evident at both predicted failure and actual patient-specific hemodynamics.

Figure 10.

Diameter changes [m] versus x location [m] of the blood vessel for (a) subject 12 and for (b) subject 32. The dashed line shows diameter changes from TM to *predicted* patient-specific failure, and the solid line shows the diameter changes from TM to *actual* patient-specific failure. The flow is from right to left. Notice the agreement between the actual and predictive computational data when D becomes negative i.e. the luminal diameter has reduced locally in the arch.

Figure 11. Evolution of the shape and the resultant restoration of WSS [Pa] at the time of failure for subject 12.

Figure 12. Evolution of the shape and the resultant restoration of WSS [Pa] at the time of failure for subject 32.

Figure 13. Evolution of the shape and the resultant restoration of WSS [Pa] at the time of failure for subject 4.

Figure 14. Evolution of the shape and the resultant restoration of WSS [Pa] at the time of failure for subject 128.

Figure 15. Evolution of the shape and the resultant restoration of WSS [Pa] at the time of failure for subject 44.

Figure 16. Maximum D obtained using various target values of WSS in the shape optimization study. The same shape occlusion and max D resulted from using multiple different target values from the cephalic vein's physiological WSS range of 0.076 to 0.76 [Pa].

Figure 17.
Three-dimensional CFD coupled with shape optimization for patient 12.

Figure 18.

The three-dimensional WSS distribution at (a) TM, at (b) failure predicted by CFD coupled shape optimization, and (c) at actual patient-specific time of failure for patient 12. Blue: $0.076 \text{ Pa} \leq \tau_w \leq 0.76 \text{ Pa}$, Red: $\tau_w \leq 0.076 \text{ Pa}$, Green: $\tau_w \geq 0.76 \text{ Pa}$.

(a)

(b)

Figure 19.
Venous bifurcation venogram at (a) TM and (b) at the time of failure. Subject number 119.

Figure 20.

Velocity magtinude [m/s] of the bifurcated case under investigation (a) at the time of failure and (b) predicted by shape optimization and CFD.

(a)

(b)

(c)

Figure 21.

WSS [Pa] distribution (a) at TM, (b) at predicted failure, and (c) at actual time of failure.

Blue: $0.076 \text{ Pa} \leq \tau_w \leq 0.76 \text{ Pa}$, Red: $\tau_w = 0.076 \text{ Pa}$, Green: $\tau_w = 0.76 \text{ Pa}$.

Figure 22. Gaussian normal distribution of four time-of-failure patient packets from our 37 ESRD patient cohort.

Table 1

Parametrization schemes for shape optimization.

Parametrization Basis Function	Functional Form & Optimization Variables
Truncated Fourier Sine Series	$d_r=\sum_{i=1}^n q_i \, d_i \sin \left(i \pi s \right)$
Modified Truncated Fourier Sine Series	$d_r=\sum_{i=1}^n d_i \left[\operatorname{abs} \left(q_i \sin \left(i \pi s \right) \right) + q_i \sin \left(i \pi s \right) \right]$
Hicks-Henne Bump Function ^[51]	$d_r=d_i \left[\sin \left(\pi s^{\frac{\log(5)}{\log(q_1)}} \right) \right]^{q_2}$
Non-Uniform Rational B-Splines (NURBS) ^[65]	$x \left(s \right) = \frac{\sum_{i=0}^n B_{i,p}(s) w_i P_i}{\sum_{j=0}^n B_{j,p}(s) w_j}$
Bernstein Basis Function ^[65,50]	$d_r=B_n \left(s \right) = \sum_{i=0}^n d_i \, q_i \, b_{i,n} \left(s \right),$ $b_{i,n} = \binom{n}{i} s^i (1-s)^{n-i}$ <p>where,</p>

Table 2

Shape parametrization schemes and the decrease in objective functional they provided in our patient-specific test case.

Parametrization Scheme	Objective Functional Improvement $\frac{N}{m}$
20 Truncated Fourier Sine Terms	From 0.451 to 0.201
Modified Truncated Fourier Sine Series	From 0.451 to 0.146
Hicks-Henne Bump Function	From 0.451 to 0.300
10 th Degree Bernstein Basis Function	From 0.451 to 0.130

Table 3

Patient-specific inlet velocity read from Doppler measurements, blood viscosity from viscometry tests of blood samples drawn, and inlet venous diameters measured from venogram for subjects 12, 32, 4, 128, and 44 at TM.

Patient Number	Inlet Velocity ($\frac{m}{s}$)	Viscosity (Pa.s)	Inlet Diamater (m)
12	0.543	0.00328	0.0045
32	0.961	0.00291	0.0038
4	1.2	0.00284	0.0039
128	0.575	0.00356	0.006
44	0.695	0.0035	0.0054