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Hemodynamics in the Cephalic Arch of a Brachiocephalic Fistula

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Abstract

The care and outcome of patients with end stage renal disease (ESRD) on chronic hemodialysis is directly dependent on their hemodialysis access. A brachiocephalic fistula (BCF) is commonly placed in the elderly and in patients with a failed lower-arm, or radiocephalic, fistula. However, there are numerous complications such that the BCF has an average patency of only 3.6 years. A leading cause of BCF dysfunction and failure is stenosis in the arch of the cephalic vein near its junction with the axillary vein, which is called cephalic arch stenosis (CAS). Using a combined clinical and computational investigation, we seek to improve our understanding of the cause of CAS, and to develop a means of predicting CAS risk in patients with a planned BCF access. This paper details the methodology used to determine the hemodynamic consequences of the post-fistula environment and illustrates detailed results for a representative sample of patient-specific anatomies, including a single, bifurcated, and trifurcated arch. It is found that the high flows present due to fistula creation lead to secondary flows in the arch owing to its curvature with corresponding low wall shear stresses. The abnormally low wall shear stress locations correlate with the development of stenosis in the singular case that is tracked in time for a period of one year.

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Conflict of Interest

There is no conflict of interest for any of the authors in this study.

Ethical Approval

This study was submitted to, and approved by the Institutional Review Board at the University of Chicago (protocol 11-0269). Informed written consent was obtained from each participant before trial onset.

Keywords

brachiocephalic; fistula; cephalic arch; intimal hyperplasia; stenosis

1. Introduction

The outcome of patients with end stage renal disease (ESRD) undergoing hemodialysis depends on a functioning vascular access. Although a variety of techniques have been developed for providing hemodialysis access, there have been no major advances for the past three decades. This contributes to the fact that hemodialysis access dysfunction is one of the most important causes of mortality in the hemodialysis population. In addition, the expense of providing ESRD care in the US is a significant portion of the Medicare budget, totaling \$32.9 billion in 2007, of which a significant portion is spent on placement and maintenance of vascular access (Collins, 2012). Obstacles to long term fistula access include prevention and maintenance of venous stenosis. This investigation considers hemodynamic contributions to the primary mode of failure, cephalic arch stenosis (CAS), for dialysis patients with a brachiocephalic fistula (BCF).

1.1. Background

Native AVF have the lowest rate of complications and are recommended for vascular access (Collins, 2012; DHHS, 2012; Besrab et al., 2006). The type of AVF with the best outcomes is the radiocephalic fistula (RCF); however, this access often fails to mature in elderly patients with underlying vascular disease, particularly in diabetics (Miller et al., 1999; Rodriguez et al., 2000). The second recommended access is the brachiocephalic fistula (BCF), which has a mean duration of function of only 3.6 years in contrast to RCF, which often exceed 5 years (Rodriguez et al., 2000).

The BCF is a high-flow conduit for hemodialysis created by vascular surgeons in which the cephalic vein is joined to the brachial artery, typically in an end-to-side or side-to-side arrangement. The cephalic arch is the final bend in the cephalic vein prior to its junction with the axillary vein. The cephalic vein and arch geometry are illustrated in Figure 1 as is the downstream connecting axillary vein. In this figure, d is the diameter, α is the cephalic arch angle, and R is its radius of curvature. The blood enters the cephalic arch from the right.

1.2. Postulated Origins of Cephalic Arch Stenosis

One of the leading hypotheses is that cephalic arch stenosis results from neointimal hyperplasia due to locally low shear stresses on the vessel wall. Research suggests the possibility that hemodynamic forces, including wall shear stress, play a critical role in the regulation of vessel diameter. The diameter changes locally in order to maintain values of the shear stresses within an acceptable or target range. This mechanism is often referred to as *adaptation* (see for example, Krishnamoorthy et al., 2008; Berger and Jou, 2000). In the presence of low wall shear stresses, the intimal layer experiences growth due to the proliferation of smooth muscle cells from the media layer. Critical thresholds of wall shear stresses for veins are provided in Table 1. The wall shear stress values for a normal vein range from 0.076 to 0.76 Pa, (Van Tricht et al., 2005). It is noted, however, that the etiology

of stenosis is primarily derived from arterial studies; therefore, it must be confirmed that the adaption process also applies to the venous system.

1.3. Clinical and Computational Studies

The leading cause of BCF failure is due to stenosis in the cephalic arch (Rajan et al., 2003). This is a recently recognized phenomenon and is often termed cephalic arch stenosis (CAS). Once CAS occurs, it leads to head and neck swelling, high venous pressures and resultant thrombosis with complex and difficult treatment options (Van Tricht et al., 2005; Hammes et al., 2008; Klan and Asif, 2008). The arch is elastic, resistant to repeated angioplasty, and often requires stent placement resulting in further stenosis. Our experience at the University of Chicago shows that CAS is a common problem among dialysis patients with BCF. A retrospective review of 97 patients with BCF over a five year period shows that CAS occurred in 77% of the subjects, with the median time to development being 779 days (CI 666 to 892) (Hammes et al., 2008). Miller et al. find that fistula flow reduction via banding of the juxta-anastomotic segment may reduce the incidence of intimal hyperplasia induced CAS in patients with BCF access (Miller et al., 2010).

There are several computational studies specifically regarding the brachiocephalic fistula. He et al. develops a protocol based on contrast-free MRI and 3D CFD for assessment of hemodynamic parameters and geometry changes in a brachiocephalic fistula. Results are provided for a single patient-specific geometry He et al. (2013). The study finds non-physiologic, disturbed flow in the AVF and spiral flow in the vein. Temporally averaged wall shear stresses were found to decrease in the vessel over the time period from 4 to 7 months. Sigovan et al. (2013) performs a study looking at the feasibility of using a noncontrast-enhanced MRI and CFD protocol to relate the hemodynamic changes to vascular remodeling over a three month time period in both brachiocephalic and brachiobasillic fistulae. In another study, Kharboutly et al. (2007) investigated the relationship between fluid flow and vascular alterations in a brachiocephalic fistula. Flow recirculation and associated negative wall shear stresses outside the normal physiological range are observed on the venous outflow side. An alternative approach to 2D or 3D modeling is a 1D network model of the fistula and connecting vessels. This approach has been recently used on various fistula configurations including the brachiocephalic (Bode et al., 2012; Caroli et al., 2013). The following related studies are also noted. Several investigations consider the flow in the radiocephalic fistula, see for example, Sivanesan et al. (1999); Niemann et al. (2010); Carroll et al. (2011). In addition, there are numerous studies where the primary emphasis is on the local modeling of the anastomosis region without considering details of the outflow (cephalic) vein. See for example, McGah et al. (2013) and references therein.

1.4. Objectives

The purpose of this research is to describe the methodology used to create patient-specific CFD models that are used to determine the hemodynamics within the cephalic vein and arch in patients with a BCF. The computational model can help elucidate the hemodynamic contributions to the etiology of cephalic arch stenosis in BCFs. More broadly, the present investigation provides a unique opportunity to investigate the influence of hemodynamics on

neointimal hyperplasia and stenosis in veins (compared to arteries where a better understanding exists) under extreme hemodynamic conditions resulting from the post-fistula environment.

2. Clinical and Computational Methods

The clinical and computational methodology used in this study involving multiple disciplines is described. Whereas similar investigations have emphasized detailed modeling (3D) of a small number of patient-specific hemodynamic flows, the present investigation develops a combination of *in vivo* measurements and computational models having short turnaround times that can be utilized in a clinical setting. In particular, the CFD model will be combined with clinically available – and cost effective – imaging technology, such as two-dimensional venograms, to develop a realistic representation of the hemodynamics within patient-specific cephalic arch geometries. Note that the use of MRI is not possible with ESRD patients owing to the toxicity of the markers used (Cowper et al., 2008). There are noncontrast MRI techniques that could be used; however, most routine MRI studies lack the spatial resolution of venography and are quite lengthy by comparison to venography, which typically is performed in 5 minutes.

2.1. Clinical Data and Imaging

After the patient is enrolled, pre-operative venogram, Doppler velocity measurement of the cephalic arch, and whole blood viscosity (WBV) are obtained. This data is again obtained at three months and one year. The venogram is performed as follows with simultaneous blood flow measurements. The patient has their fistula punctured with a 21-gauge needle near the arterial anastomosis directed toward the stenosis (either venous or arterial). The needle is exchanged for a 5 French dilator, and a digital subtraction venogram encompassing the outflow from puncture site to the right heart is performed. Any stenosis is measured using electronic calipers and defined. Any significant hemodynamic stenosis, defined as greater than 50% narrowing of the expected luminal diameter (75% by area), is treated with balloon angioplasty according to DOQI consensus from the International Society of Interventional Radiology (Depner and Daugirdas, 2006).

Doppler spectral analysis is performed by an interventional radiologist at the time of each venogram to measure velocity in the cephalic vein. The peak systolic velocity (PSV) at a 60-degree angle of insonation is measured in the straight portion of the cephalic vein between the anastomosis and the arch, approximately 10 cm proximal (upstream) of the cephalic arch. The velocities in this location are measured over several heart cycles and the average calculated.

WBV is measured using blood samples obtained from patients at baseline, three months, and then one year. The blood is drawn during IV insertion or routine lab draw and is collected in a 4.5 ml tube containing 3.2% buffered sodium citrate. The blood is diluted to 1/10 volume of 108 mM sodium citrate with the volume of anticoagulant constant for each sample. The blood samples are kept on ice and transported to IIT for assay. WBV is measured at various shear rates 10 s^{-1} to 780 s^{-1} at 37 C using a Brookfield Programmable DV-II+ cone plate viscometer. The viscosity at 220 s^{-1} is used in the CFD simulations.

The total number of patient-specific measurements thus far is 29, 35, and 15 for 0, 3, and 12 months post-fistula creation, respectively. Average values of geometric and hemodynamic parameters are provided in Table 2. Typical results are provided in Section 3 and include: (1) single vessel hemodynamics evolution with time (Sec. 3.1), (2) hemodynamics in a vessel bifurcation (Sec. 3.2) and (3) vessel trifurcation (Sec. 3.3).

2.2. Geometry Reconstruction

The procedure for converting radiologic images into a geometry file for use in the CFD is a two step process. The first step is at the image pixel level where the noise in the grayscale radiological images is suppressed and the edges that define the cephalic vein boundaries are extracted. The Wiener filter is used for noise removal and Canny edge detection for extracting edge pixels. The second step is at the 2D Euclidean space level, where cubic B-spline curves are reconstructed out of the extracted edge pixels. A least-square method is used for reconstructing the B-spline curves. The reconstructed B-splines are then written into the IGES file format. Figure 2(a) shows an example of vessel wall or boundary identification using the pixel-based method. The red curves are reconstructed B-spline representations of the vein boundaries and blue points are the corresponding B-spline control points. This geometry is then imported into the grid generation tool Gmsh, where it is meshed to create the spectral elements (Geuzaine and Remacle, 2009). See Figure 2(b) for an example of a patient-specific geometry (from Figure 2a) after import into Gmsh. See Figure 2(c) for an example of a patient-specific mesh. The mesh is then read into either CFD solver, Nek5000 or COMSOL.

2.3. Computational Fluid Dynamics Model

The mathematical model governing the hemodynamics in the cephalic vein and arch is the unsteady, incompressible continuity and Navier-Stokes equations. In non-dimensional form they are,

$$\nabla \cdot \mathbf{v} = 0, \quad (1)$$

$$\frac{\partial \mathbf{v}}{\partial t} + \mathbf{v} \cdot \nabla \mathbf{v} = -\nabla p + \frac{1}{Re} \nabla^2 \mathbf{v}. \quad (2)$$

Here, $\mathbf{v}$ is the velocity vector with axial and lateral components $u(x, y, t)$ and $v(x, y, t)$, respectively, and $p(x, y, t)$ is the pressure. The above equations can be non-dimensionalized using the half-channel height at the inlet, h , as the characteristic length-scale and the measured patient-specific mean inlet velocity, U , upstream of the arch. The non-dimensional Reynolds number is $Re = \rho h U / \mu$, where ρ is the density of the blood taken to be 1050 kg/m^3 , and μ is the measured patient-specific dynamic viscosity. The half-channel height h is used for the simulations corresponding to the measured patient-specific radius of the cephalic vein.

The flow of blood in the cephalic vein is assumed to behave as a homogeneous (single phase and species) Newtonian fluid, and the vessel walls are assumed to be rigid. As part of this study, an evaluation of several commonly employed non-Newtonian models for blood is

performed using measured viscosity and shear-rate data from this investigation. Based on previous studies and reviews of hemodynamic and stenotic flows, vessel wall motion (fluid-structure interaction) is often considered a secondary effect (Wootton and Ku, 1999). However, it is intended to include wall motion in a future study.

The region of interest in this study is an approximately 10 cm segment of the cephalic vein. The domain starts downstream of the anastomosis in a relatively straight segment of the cephalic vein. Thus, this model does not contain any detail of the anastomosis geometry. As noted by McGah et al. (2013), the flow dynamics in the anastomosis has an effect on the inflow conditions to the cephalic vein. If there are recirculation regions in or upstream of the anastomosis, their global effects are included in this model. Any such regions would result in reduced flow rates into the cephalic vein. The velocity is measured in the cephalic vein located downstream of the anastomosis. Thus, any reduced flow rates resulting from anastomosis hemodynamics are accounted for. The velocity measurement location may not be far enough downstream from the anastomosis to justify imposing a fully developed flow at the inlet of the cephalic vein. However, the focus here is on the downstream cephalic arch hemodynamics. As such, a steady, parabolic flow is a reasonable inlet condition because the flow will have adequate length to develop/adjust prior to entering the arch. In future studies, the effect of flow pulsatility will be considered. The domain ends at the T-junction with the axillary vein. Boundary conditions need to be imposed at the outlet, but the flow and pressure are not known there a priori. Thus, a standard outflow boundary condition is assumed. As a result, there will be some local region near the outflow where the computational model may not be accurate. However, this will not adversely affect the predictions upstream in the arch. Thus, the boundary conditions at the inlet are

$$u(y) = \frac{3}{2}(1 - y^2), v = 0, \quad (3)$$

and the no-slip and impermeable conditions are enforced on the channel walls such that $u = v = 0$. For the initial condition, the flow is assumed to start from rest. The unsteady, incompressible Navier-Stokes equations subject to the initial and boundary conditions are integrated in time using a CFD code. Currently, the option to use two different Navier-Stokes solver codes, Nek5000 and COMSOL Multiphysics, is available in the present study. The spectral element code, Nek5000, was developed at the Argonne National Laboratory (Fischer et al., 2002, 2008). This open source code is actively developed and has been extensively tested for many years. The commercially available multiphysics finite-element code, COMSOL, is also used. COMSOL, like Nek5000, is also a mature, well-tested code developed in the 1990s. Both CFD tools have been used in biofluid applications for years, and the codes have been verified by comparisons to both analytical solutions and experimental data.

Grid resolution studies have been performed by doubling the number of nodes in each direction until grid-independence has been achieved. For the two-dimensional simulations below a Reynolds number of approximately 700, the average number of degrees of freedom is close to 100,000. For Reynolds numbers above 700, there are approximately 300,000

degrees of freedom owing to the unsteady vortex shedding and small-scale structures that are present, see for example, Boghosian and Cassel (2013).

3. Results

Numerical simulation results are presented illustrating various representative types of cephalic vein anatomies (*i.e.* single arch and arch bifurcations to two and three branches) observed thus far from the venograms. The results in the normal anatomy are obtained with Nek5000, and the results for the bifurcation and trifurcation cases are found with COMSOL.

3.1. Cephalic Arch Type 1: Singular (no bifurcations)

The first case shows a single cephalic arch with a time sequence of results for a patient undergoing dialysis for a period of one year (data at 0, 3, and 12 months). Figure 3 shows venogram images depicting the evolution of the vein geometry and stenosis from baseline ($t = 0$) to a time of one year. The first image in part *a*, prior to fistula creation, shows a typical cephalic arch. Flow enters from right to left and exits at the axillary vein junction and no stenosis is observed. The next two images, parts *b* and *c*, show that most of the cephalic arch has become stenosed at some point in time between 3 and 12 months.

The arch angle, radius, average inlet velocity, viscosity and Reynolds number (based on the inlet radius and average velocity) are shown in Table 3 as a function of time for the same patient shown in Figures 3 and 4. Streamlines from the CFD simulations are shown in Figure 4 for various time points. As expected at this Reynolds number, prior to fistula creation ($t = 0$) the flow is laminar, steady, and no separation is observed. The computed minimum and maximum wall shear stresses are 0.093 Pa and 0.593 Pa , respectively, which are within the normal range for a vein as shown in Table 1. Thus, the predicted flow behavior is consistent with normal physiological behavior in a vein prior to fistula creation.

The geometry three months after fistula creation is shown in Figure 3*b*. By this time, the vein is acting like an artery as it experiences increased pressures and flow rates due to bypassing some of the lower arm resistances. The arch angle has remained about the same over the three months time period. Note that based on the patient database in Table 1, this is not typical. The average arch angle decreases by approximately 16 degrees by the 3 month timeframe. The mean inlet velocity increases by a factor of 10. The Reynolds number has now increased to $Re = 261$, a factor of approximately 12 compared to pre-fistula. Although this value is well beyond the normal physiological Reynolds number for the cephalic vein, the flow remains laminar and steady. However, now there is flow separation in the arch as the low momentum fluid near the walls cannot overcome the local adverse pressure gradient. A recirculation region is observed near the upper wall in part *b* of Figure 4. As noted in Table 1, the low wall shear stresses associated with secondary flows may initiate the start of intimal hyperplasia and ultimately stenosis. At this time, the minimum wall shear stress decreases to -0.346 Pa (corresponding to reversed flow) and the maximum increases to 7.1 Pa . Thus, at a time of 3 months after fistula creation, the flow and resulting mechanical stresses are already beyond the normal physiological range. The separated flow present at this point in time appears to have a minor effect as a limited amount (and spatial extent) of

neointimal hyperplasia is observed in the arch immediately prior to the recirculation region. However, this region will be looked at closely at the 12 month time period.

The geometry at 12 months post fistula is shown in part *c* of Figure 3. The arch angle is found to be unchanged, which is somewhat consistent with the average data from Table 2. Again, there are recirculation regions present towards the arch outlet. However, now most of the arch shows significant stenosis compared to 3 months.

At this 12 month time, the Reynolds number increased to $Re = 462$. The flow remains laminar and steady but is close to the unsteady threshold based on previous simulations in Boghosian and Cassel (2013). Multiple recirculation regions are observed on both walls near the end of the arch as seen in part *c* of Figure 4. In the arch region, the minimum wall shear stress decreases to $-16.8 Pa$ and the maximum increases to $97.54 Pa$. Both of these extremum exceed the normal physiological wall shear stress range as shown in Table 1. In addition to further neointimal hyperplasia, it is possible that endothelial damage, such as denudation, is taking place where the levels are above $40 Pa$.

A combined streamline and wall shear stress plot helps interpret the hemodynamics predicted by the CFD. Figures 5 and 6 show locations on the cephalic vein walls where the shear stress is below the low end of the normal range ($0.076 Pa$, marked with bold, pink lines) and where the shear stress is above the threshold for endothelial denudation ($40 Pa$ marked with bold, purple lines). In part *b* of this figure, it can be seen that most of the arch has locations below the critical value postulated for neointimal hyperplasia. According to the hypothesis, the arch should experience neointimal hyperplasia. In Figure 6, the streamlines and critical wall shear stress regions are shown at a time of 12 months. The regions below the critical at the 3 months time period are now observed to have experienced significant stenoses. In addition, there remains several regions near the outlet below the critical threshold. Here, it appears that either a vessel aneurysm has developed or there is incomplete vessel adaption. Also, there are two locations on each wall in the arch where the shear stress levels are above the endothelial damage range ($40 Pa$), denoted by the purple color. Thus, in the single case tracked over time, the hypothesis between the presence of low wall shear stresses and the future development of neointimal hyperplasia appears to be valid.

At larger Reynolds numbers that may occur in the future, and also assuming the existing stenoses remains approximately the same, it is expected that the velocity profiles and shear-layers will become unstable leading to time-dependent behavior involving vortex shedding and shear-layer fluctuations as discussed in Boghosian and Cassel (2013). This patient will continue to be followed in time and a model will be made of the cephalic vein and arch at 24 and 36 months post fistula.

3.2. Cephalic Arch Type 2: Bifurcation

The cephalic vein is occasionally observed to bifurcate, or branch, into two distinct flow paths prior to joining the axillary vein. A definition of cephalic vein bifurcation is provided by Klan and Asif (2008). These authors define cephalic vein bifurcation as when the vessel splits with both branches either draining into the axillary vein, or when one branch joins the axillary vein and the other branch joins the external or internal jugular. At this point in the

study, five cephalic vein bifurcations and one cephalic vein trifurcation are observed prior to fistula creation.

Figure 7 shows a representative example of a patient-specific cephalic arch that bifurcates into two vessels. A comparison of parts *a* and *b* in this figure indicate that the angle of one branch of the cephalic arch becomes more acute similar to the single arch case, again possibly due to the increased pressure in the cephalic vein compared to pre-fistula.

Numerical simulations are performed for a bifurcation case at a time of 12 months after fistula insertion with the computational grid shown in Figure 8. The mean inlet flow is measured to be $= 52.5 \text{ cm/s}$ from Doppler ultrasound. The inlet vessel radius is 0.225 cm from the venogram. The dynamic viscosity is measured to be 2.88 cP . Using a density of 1050 kg/m^3 gives a Reynolds number of $Re = 430$. The simulation is found to be unsteady at this Reynolds number for this patient-specific geometry.

A plot of the streamfunction contours in Figure 9 reveals unsteady vortex shedding behavior in the upper flow branch. The lower branch also shows unsteady behavior, where the recirculation regions are observed to split and merge in time and have small lateral movement or oscillation, but no shedding. A consequence of vortex shedding is reversed flow and low (negative) wall shear stresses occur on the wall for a portion of time. This is identified in part *a* of the figure where wall shear stress locations below the critical are shown in red. Also, another interesting flow feature is the large recirculation region at the inlet to the lower branch. This flow structure acts to reduce the effective flow area. Thus, the volumetric flow in this branch is reduced from the potential maximum where no vortex is present at the inlet. Part *b* of this figure shows the wall pressure distribution. This case has a functioning fistula at 12 months even at the elevated Reynolds number. More data will be obtained at 24 and 36 months.

3.3. Cephalic Arch Type 3: Trifurcation

The venograms also show a cephalic vein branching into three distinct flow paths in one patient. Figure 10 shows an example of this type of cephalic arch (flow is from right to left). The Reynolds number is $Re = 405$ based on the measured average inlet velocity and radius. Numerical simulations are again performed at a time of 12 months after fistula insertion. This case is found to have a steady solution at this Reynolds number for this patient-specific geometry and general conclusions are similar to the bifurcation case.

A plot of the streamfunction contours in Figure 11 again shows a number of stationary recirculation regions. A large recirculation region is observed at the inlet of the lowest branch that severely restricts flow into that branch. The middle branch also experiences a reduction in effective flow area due to this recirculation region. The effect of this area reduction can be seen in Figure 12 where the velocity magnitude is lower in the middle branch, and still lower in the lowest branch indicating that less volumetric flow is entering these branches. However, it is believed that having a bifurcation or multiple branches is protective compared to not having a bifurcation as a branching flow path has a lower volumetric flow rate than in a single vessel and thus less likelihood of flow separation and

low wall shear stresses. This case has a functioning fistula at 12 months. More data will be obtained at 24 and 36 months.

4. Discussion

The CFD simulations show that both increased volumetric flow rate post-fistula and cephalic arch geometry have a significant effect on the hemodynamics within the cephalic arch. Although the dramatically increased blood flow at the time of fistula creation leads to a corresponding increase in the overall shear stresses experienced by the cephalic vein, localized shear stresses in the cephalic arch can be lower than normal physiological values owing to localized reversed flow conditions that can arise in curved vessels at the high fistula flow rates. This may lead to the development of neointimal hyperplasia in order to adapt the vein such that wall shear stress returns to physiologically acceptable values. The data for the single vessel case is consistent with this hypothesis. However, more data from a large patient population is being obtained to confirm this.

The cephalic vein bifurcation and trifurcation anatomies appear to be protective with respect to developing neointimal hyperplasia and stenosis. This is true even though Figures 9a and 11a shown more areas where the wall shear stress is below the critical value compared to Figure 6. This may be because the minimum values of wall shear stress are lower (more negative) in the single vessel case. By providing alternative flow paths, these additional branches reduce the individual branch inlet flow velocity and the possibility of recirculation regions, and associated nonphysiological wall shear stresses. The data obtained thus far shows that all patients (100%) with flow branching (bifurcation and trifurcation cases) have a working fistula at 12 months. On the contrary, 40% of the patients (6/15), without cephalic arch branching are found to have stenosis at 12 months.

A possible explanation of the observed vein evolution shown in parts *b* and *c* of Figure 3 (corresponding stream-function plots in Figure 4) is termed the “propagating intimal hyperplasia” hypothesis. It suggests that given a sufficient stenosis, the environment immediately downstream consisting of the recirculation regions contains low wall shear stresses, and thus neointimal hyperplasia is likely to occur there based on the low shear stress hypothesis. This can develop into an extension of the original stenosis and the process repeats with low wall shear stresses and associated neointimal hyperplasia continuing down the vessel length. This may be occurring at the 3-month time period shown in part *b* of Figure 4.

The venous wall remodeling due to increased venous pressures appears to end by three months after fistula creation in the anastomosis region of a radiocephalic fistula as noted by McGah et al. (2013). It is found that neointimal hyperplasia and subsequent stenoses in the cephalic vein outflow segment typically do not occur prior to three months. Thus, if the two regions are assumed to behave similarly, the neointimal hyperplasia may be driven by the low wall shear stress hypothesis (adaption) rather than pressure-based venous wall hypertrophy hypothesis (remodeling).

Current CFD can account for three dimensional, non-Newtonian, and fluid-structure interaction effects in research environments. However, such calculations impose severe computational requirements for each individual simulation (Lee et al., 2001; Loth et al., 2003). Therefore, various compromises must be made in applying CFD technology in clinical environments where there is a high volume of subjects and the need for fast turnaround times. One clinical application of CFD with these requirements is the hemodialysis fistula. The clinical and computational methodology developed here is tailored to both the clinically available patient-specific information, e.g. the 2D venograms (no extra MRI needed) and fast simulation run-times. Nonetheless, 3D modeling is performed on a small subset (≈ 10) of the subjects to assess the impact of three-dimensional effects (to be reported separately).

By design this study focuses on the wall shear stress-intimal hyperplasia connection as the primary cause of cephalic arch stenosis. Other factors may contribute to the arch stenosis include pulsatility, vessel wall motion, cholesterol, inflammatory chemicals, and hypoxia. Not including these factors in the model may be a limitation of the study.

5. Summary

Traditional surgical methods for BCFs have not benefited from a better understanding of the consequences of fistula creation on the hemodynamics within the cephalic arch. The methodology put forth in this research demonstrates that widely available and cost-effective tools can be used to develop patient-specific CFD models of hemodialysis fistulae and predict local and global hemodynamic parameters. The results here are consistent with the hypothesis that local regions of low wall shear stress in the cephalic vein outflow segment correspond with the development of neointimal hyperplasia. This finding is also in agreement with other researchers where recent evidence suggests that the low wall shear stress hypothesis may play an important role in anastomoses failures (McGah et al., 2013).

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Figure 1.
Geometric parameters characterizing the cephalic arch (C is the cephalic vein; A is the axillary vein). Arch angle (α); Radius of curvature (R); Diameter of cephalic vein (d).

(a) Venogram image with spline control points.

(b) Reconstructed geometry.

(c) Gmsh spectral-element mesh.

Figure 2.

(a) Example of patient-specific venogram image illustrating pixel-based method used to identify cephalic vein boundaries. Note for visualization purposes only some of the control points and a portion of the mesh are shown. (b) Reconstructed geometry. (c) Gmsh spectral-element mesh.

(a) 0 Month

(b) 3 Months

(c) 12 Months

Figure 3.

Venogram images showing patient's cephalic vein and arch at various times after fistula creation.

Figure 4.
Streamlines in cephalic arch at various times since fistula creation for same patient.

Figure 5. Critical wall shear stress regions at $t = 3$ months. Solid, bold, pink line denotes locations where shear stresses are $< 0.076 \text{ Pa}$.

Figure 6. Critical wall shear stress regions at $t = 12$ months. Solid, bold, pink line denotes locations where shear stresses are $< 0.076 \text{ Pa}$. Solid, bold, red line denotes locations where shear stresses are $> 40 \text{ Pa}$.

(a) Prior to fistula creation.

(b) 12 months after fistula creation.

Figure 7.

Venogram images for bifurcated arch before and post-fistula creation. Note changes in angle of the upper branch in part (b).

Figure 8.
Example mesh for cephalic arch bifurcation case at $t = 12$ months.

(a) Critical wall shear stress regions (< 0.076 Pa) superimposed on streamlines. Critical regions are denoted with solid, red lines.

(b) Pressure contours superimposed on streamlines. Pressure contours on wall range from 6 to 11 mmHg.

Figure 9.

Instantaneous streamlines for bifurcated cephalic arch case at 12 months post-fistula creation.

Figure 10.
Example of cephalic arch trifurcation case at $t = 12$ months.

(a) Critical wall shear stress regions (< 0.076 Pa) superimposed on streamlines. Critical regions are denoted with solid, red lines.

(b) Pressure contours superimposed on streamlines. Pressure contours on wall range from -0.5 to 1.2 mmHg.

Figure 11.

Instantaneous streamlines for trifurcated cephalic arch case at 12 months post-fistula creation.

Figure 12. Velocity magnitude contours for cephalic arch trifurcation case at $t = 12$ months. Contour levels range is from 0 to 0.6 m/s with 6 increments.

Table 1

Critical wall shear stress levels for normal veins (Berger and Jou, 2000; Van Tricht et al., 2005; Slack and Turitto, 1993; Turitto, 1982).

Condition	Critical WSS Levels (Pa)
Postulated intimal hyperplasia	< 0.076
Vein (minimum)	0.076
Vein (maximum)	0.76
Endothelial denudation	> 40

Table 2

Average values of geometric and hemodynamic parameters as a function of time: (a) before BCF creation (0 months), (b) three months and (c) twelve months after the fistula procedure.

Parameter	0-Month	3-Month	12-Month
Arch angle, α	135°	119°	117°
Vein diameter, d	2.8 mm	4.7 mm	5.5 mm
Avg. velocity, u	4.1 cm/s	42.7 cm/s	69.1 cm/s
Viscosity, μ	3.07 cP	3.26 cP	3.14 cP
Reynolds No., Re	16	347	729

Table 3

Cephalic vein and arch parameters as a function of time since fistula creation for single patient corresponding to Figures 3 and 4.

Parameter	0-Month	3-Month	12-Month
Arch angle, α	119°	120°	120°
Vein radius, r	1.8 mm	2.25 mm	2.0 mm
Average inlet velocity,	3.7 cm/s	36.2 cm/s	58.5 cm/s
Viscosity, μ	3.34 cP	3.28 cP	2.66 cP
Reynolds No., Re	21	261	462