CHAPTER 5

5 ANALYSIS OF GEOMETRIC ALTERNATIVES INTENDED TO IMPROVE DISTAL ANASTOMOTIC PATENCY

5.1 Introduction

The widely accepted view that hemodynamic factors initiate a biophysical cascade that is ultimately responsible for distal anastomotic intimal hyperplasia (DAIH) suggests that geometric modifications may significantly improve distal anastomotic performance. Considering the problematic below-the-knee distal femoral anastomosis (Fig. 4.1.1), clinical evidence indicates that inter-positioned vein cuffs (Miller et al., 1984; Stonebridge et al., 1997; Fig. 4.1.3b) and vein patches (Taylor et al., 1992; Fig. 4.1.3c) significantly extend graft function. A number of potential surgical, hemodynamic, and biological mechanisms have been associated with the improved patency of vein-supplemented designs (Stonebridge et al., 1997; Harris and How, 1999; Noori et al., 1999; Leuprecht et al., 2002); however, no single factor appears responsible. While clinical results appear promising, wide-spread implementation of vein-supplemented designs has been limited by the surgical rigor associated with constructing a cuff or patch as well as the presumed increased risk of surgical complications and technical errors. In an effort to expedite the surgical procedure and further mitigate inciting hemodynamic factors, several researchers have suggested the implementation of expanded grafts (Lei et al., 1996 & 1997; Harris and How, 1999; Longest and Kleinstreuer, 2000; Longest et al., 2000; cf. Fig. 5.1.1). As a result, expanded graft-end configurations are now commercially available under the trade names Venaflo™ and Distaflo™ (Impra Bard, Tempe, AZ). Preliminary clinical trials indicate moderate improvements in the patency of the pre-cuffed Distaflo™ configuration (39% patency after one year; Fisher et al., 2002); however, as with the vein supplemented designs, the specific biophysical pathways responsible for improved performance have not been identified.

Focusing on the Miller design, Stonebridge et al. (1997) found no improvement in patency associated with cuffed above-the-knee popliteal artery bypass grafts. However, patency rates were significantly improved for the Miller cuff positioned at the below-the-knee popliteal artery in comparison to un-cuffed configurations. Qualitative angiograms and pathological studies of human (Tyrrell and Wolfe, 1997) and animal (Kissin et al., 2000; Leuprecht et al., 2002) Miller style grafts indicate that a potential mechanism for improved graft performance is the redistribution of DAIH occurrence away from critical areas, such as the arterial heel, toe, and floor. Most significant DAIH is observed at the cuff-to-graft interface of the Miller design, where it is better accommodated by the larger cross-sectional area. The observed shift in DAIH occurrence is particularly significant considering the smaller arterial diameters associated with below-the-knee procedures and may potentially account for the improved patency rates reported for the cuffed geometries at this location.

Biophysical and computational studies of the Miller cuff have suggested that higher wall stresses, reduced compliance mismatch, and the biological effect of a natural ‘buffer zone’ may account for the reported higher long-term success rates of the vein supplemented design (Harris and How, 1999; Leuprecht et al., 2002; Kissin et al., 2000). Noori et al. (1999) and Harris and How (1999) have suggested that vortical flow engendered by the Miller configuration provides a beneficial ‘continuous washout’ of the cuff cavity and elevates wall shear stress (WSS) along the arterial floor. However, the hemodynamic and mechanical advantages of the Miller cuff have been widely questioned. For example, Cole et al. (2002b) found that aspects of the anastomotic hemodynamics were worsened with the cuffed configuration. Kissin et al. (2000) showed that considerably more DAIH formed in a PTFE cuffed anastomosis compared to a vein cuff, which indicates that anastomotic hemodynamics may not be responsible for the improved clinical performance of the Miller configuration. While Leuprecht et al. (2002) suggested that compliance mismatch was responsible for the observed shift in DAIH formation, Norberto et al. (1995) found no difference in IH formation between vein cuffs and cuffs whose compliance was altered. These observations result in the conjecture that the beneficial effect of cuffed anastomoses at the below-the-knee location is not hemodynamic or mechanical in nature. Instead, it is possible that the inclusion of a natural, less thrombogenic ‘buffer zone’ close to the artery reduces a biochemical hyperplasic response along the arterial suture-line (Stonebridge et al., 1997; Kissin et al., 2000; Cole et al., 2002b). Furthermore, Stonebridge et al. (1997) observed that the reported improved patency of the Miller cuff position at the below-the-knee popliteal artery was primarily due to early graft failures of the conventional anastomoses associated with technical errors. They suggested that joining a vein segment to the artery facilitates the surgical procedure and results in a higher likelihood of a technically sound anastomosis. However, the advantages of an autogenous buffer zone and improved sutureability are not realized with pre-cuffed PTFE grafts, causing some to suggest that the benefits of these designs may be limited (Cole et al., 2002b; Kissin et al., 2000).

In an effort to improve distal anastomotic performance, Lei et al. (1996 & 1997) showed that large anastomotic flow areas, small continuously changing bifurcations angles, and smooth junction wall curvatures reduced hemodynamic wall parameters including the WSSG and OSI. They suggested an ‘optimized’ S-shaped configuration intended to minimize adverse ‘disturbed flow’ characteristics associated with DAIH (Fig. 5.1.1a). Following the lead of Lei et al. (1996), Harris and How (1999) proposed a pre-shaped PTFE cuff intended to eliminate the need for vein collar construction. While the design objective of Lei et al. (1996 & 1997) was to reduce disturbed flow patterns in the junction region, the pre-shaped cuff design of Harris and How (1999) was intended to increase vortical flow and wall shear stress (Figure 5.1.1c). Harris and How (1999) claimed the pre-shaped cuff eliminates regions of low WSS; however, no quantitative details in support of this argument have been provided. Longest and Kleinstreuer (2000) linearly combined several WSS-based hemodynamic wall parameters into one ‘severity parameter’ for analysis of an arteriovenous (AV) bypass configuration. Based on severity parameter mitigation, an ‘optimized’ AV distal anastomotic configuration was proposed (Fig. 5.1.1b).

Indeed, clinical performance of anastomotic configurations designed to hemodyamically mitigate restenosis depends largely on the appropriateness of the wall parameters analyzed. While the pre-expanded designs of Lei et al. (1996) and Longest and Kleinstreuer (2000) successfully mitigated the hemodynamic parameters considered, e.g., the

WSSG, recent findings strongly indicate multiple pathways for DAIH formation. For instance, expanded designs significantly reduce changes in WSS magnitude and direction by providing larger anastomotic areas to accommodate flow redirection. A down-side of this strategy is lower WSS-values, which has been widely associated with DAIH development (Pearson, 1994; Harrison et al., 1996; Keynton et al., 2001). Results of the current study indicate that significant interactions between critical blood particles and the vascular surface provide an extremely aggressive pathway for DAIH development (Sect. 3.6). Furthermore, regions of low WSS and lumenal vortical patterns cannot effectively determine regions of micro-scale particle-wall interactions including adhesion. Therefore, analysis of WSS conditions and 'persistent vortex' formations may result in an insufficient model for DAIH formation as well as for graft design. Significant hood curvatures, which characterize the pre-expanded configurations (Fig. 5.1.1), are expected to result in elevated particle-wall interactions along the graft surface in the region of the anastomosis. For example, the low-angle configuration of Graft 3 in the previous chapter (cf. Fig. 4.2.2) is characterized by a continuous and relatively smooth hood curvature. Nevertheless, significant particle-wall interactions were observed along the graft surface (Fig. 4.3.8f), which were consistent with the DAIH observations of Loth et al. (2002). Considering particle-wall interactions as a potential mechanism for DAIH formation, alternative anastomotic designs may be necessary.

As discussed previously, results of the current study suggest that the hemodynamic factor expected to most aggressively elicit a localized hyperplasic response within the distal femoral anastomosis is the composite NWRT model for platelets including surface reactivity and platelet activation conditions (cf. Sects. 3.3, 3.6, and 4.4.1). Monocyte interactions with the vascular surface in regions of low-WSS also have the potential to incite DAIH formations. As supported by a number of studies at the cellular level, endothelial response to regions of significantly low WSS are considered a second pathway for DAIH development. Highly focal regions of significantly elevated WSSG and WSSAG values provide a third inciting mechanism for localized IH formation. Factors such as compliance mismatch, intramural stress and strain, surgical injury, and technical errors have not been directly assessed in this study.

Based on a multi-pathway model of DAIH formation, the current analysis will focus on unexpanded anastomotic designs intended to mitigate occlusive formations. It is proposed that the unexpanded configurations may potentially minimize particle-wall interactions without significantly reducing WSS and elevating particle residence times. As a basis for comparison, the clinically successful Miller cuff will also be analyzed. As indicated in Chapter 4, the particle-hemodynamic effects of various graft and arterial curvatures, as well as the absence of proximal outflow, will be investigated.

5.2 Systems

Of interest are realistic and virtually prototyped distal anastomoses intended to reduce DAIH formations. Models include the clinically viable Miller cuff, as well as smooth unexpanded virtual prototypes with graft-to-artery diameter ratios of 1.5:1 (Fig. 5.2.1). The Miller configuration has been constructed using a straight 45^{o} graft-end cut, consistent with Graft 2 (cf. Chapter 4), and a 4 mm high venous cuff. In comparison to Graft 2 (Fig. 4.2.2), the inclusion of an inter-positioned cuff results in less axial distortion of the distal artery region. In contrast, virtually prototyped models (Fig. 5.2.1) implement a smoothly curved inlet-graft intended to gradually redirect the flow and potentially reduce disturbed hemodynamic conditions, particularly in the immediate junction area. Similarly, curvature of the recipient artery allows for a smooth transition, which is intended to redistribute IH away from regions critical to anastomotic flow delivery. Models A and B are characterized by high- and low-angle ‘concave-up’ grafts, whereas Model C represents a low-angle ‘concave-down’ configuration (Fig. 5.2.2). In contrast to the previously expanded anastomotic configurations (Fig. 5.1.1), utilizing both proximal and distal graft and arterial curvatures allows for smoothly connected unexpanded junctions intended to mitigate disturbed flow occurrence without reducing critical WSS-values and elevating particle residence times.

A transient Type I input pulse, consistent with post-surgical observations of the femoral bypass (Okadome et al., 1991), has been implemented for all grafts (cf. Fig. 5.2.3). As described in Sect. 2.2.1, the input pulse selected is well within the range of typical mean flow-rates for 6 mm femoral bypass grafts, and falls within peak velocity and Reynolds number guidelines for non-stenosed grafts (Nielsen et al., 1993; Papanicolaou et al., 1996). Consistent with Type I waveforms, only a small amount of net retrograde flow is observed, which occurs around t/T = 0. The resulting velocity profiles display a significant amount of retrograde flow in the near-wall region throughout diastole. With respect to anastomotic flow division, distal-to-proximal outflow ratios of 80:20 and 100:0 have been implemented. The former ratio is representative of conditions where flow delivery is provided distal to the anastomosis, and the latter scenario implies that the distal region is totally occluded.

5.3 Results

5.3.1 Anastomotic Hemodynamics

Mid-plane and cross-sectional contours of velocity magnitude as well as mid-plane velocity vectors for the Miller cuff and Models A – C, during accelerating (t_1; Fig. 5.3.1) and decelerating (t_2; Fig. 5.3.2) flow, illustrate the complex vortical patterns inherent to distal anastomotic configurations. In order to characterize fluid motion in the displayed cross sections, secondary velocity vectors have been used to compute surface streamlines for two-dimensional (2-D) slices (Ethier et al., 2000; Tobak and Peake, 1982). Due to the 3-D nature of the underlying flow, conservation of mass is not satisfied between adjacent 2-D streamlines. Nevertheless, the 2-D traces provide an effective representation of the underlying secondary motion at an instant in time including axial vortices and regions of flow separation (Figs. 5.3.1 & 5.3.2).

Considering the Miller-style anastomosis during flow acceleration (t_1; Fig. 5.3.1), a relatively large area is available for flow redirection, which well accommodates flow reversal associated with proximal outflow. Due to enhanced momentum transport arising from the increased viscosity in the low-shear cuff region, recirculation is not apparent at time t_1. Separation is observed in the toe region resulting in a significant axial vortex evident at Slice B. However, the underlying axial velocity in the region of the vortex is relatively high, such that reduced particle-wall interaction should result from secondary motions. Due to inlet curvature, the upstream velocity profile entering the Miller cuff at time t_2 is skewed toward the upper graft surface (Fig. 5.3.2). The condition of proximal outflow results in significant separation in the distal region of the graft-to-vein interface. The combination of a forward located stagnation point and flow expansion across the lateral suture-line results in significant recirculation in the Miller cuff sinus region, evident in Slice A. As with accelerating flow, recirculation in the mid-plane is not largely evident within the cuff cavity at time t_2. Significant separation and recirculation near the toe is accompanied by strong secondary vortices, which coincide with regions of elevated axial flow.

Considering the virtually prototyped configurations at time t_1, it appears that viscous effects dominate the centripetal forces associated with the curved inlet configurations, resulting in a relatively blunt and symmetric velocity profile just upstream of the anastomosis (Fig. 5.3.1). As such, anastomotic hemodynamics are relatively uniform among Models A – C at time t_1. However, the effects of inlet graft curvature become apparent during flow deceleration (t_2; Fig. 5.3.2). The concave-up configurations, Models A and B, result in inlet velocity profiles that are skewed toward the lower graft surface, while the inlet profile is reversed for Model C. Low pressure within the proximal segment effectively shifts the core of highest velocity flow away from the toe area such that significant mid-plane recirculation is observed for all virtually prototyped models. This effect is most pronounced for Model A, due to the significant curvature of the graft. A circumferential pressure gradient arises between the low pressure recirculation near the toe and the area of stagnation along the arterial floor, resulting in clockwise helical flow in all virtually prototyped models (cf. Slice A, Fig. 5.3.2). Secondary vortical motion appears most extensively in Model A, where a counter-rotating vortex is induced, and least significantly in Model C. The reduced secondary motions in Model C arise from the relatively mild stagnation region and smooth flow transition in the presence of proximal outflow. In contrast to the Miller configuration, secondary vortical motion is observed to occur in a region of reduced axial velocity for Models A – C.

Selected monocytes within the Miller configuration (Fig. 5.3.3a), initialized upstream over one input pulse, indicate relatively little recirculation within the cuff region. Moreover, the construction of the cuff apparently (a) provides an expanded anastomotic area to accommodate flow reversal as required for proximal outflow, and (b) allows for hemodynamic boundary zones which reduce interactions between the high concentration core of fast moving particles and the anastomotic surfaces.

Monocyte trajectories in Models A – C indicate significant helical motions emanating from the stagnation point and continuing along the lateral wall region toward the recirculation zones at the toe and heel (Fig. 5.3.3b-d). Near the toe region, significant axial velocities apparently sweep these spiraling and potentially activated particles downstream. The effect of proximal outflow appears to result in significant particle-wall interactions for all models considered.

5.3.2 WSS-Based Hemodynamic Parameters

Considering the Miller cuff, low WSS and high OSI regions are observed along the distal graft-to-vein junction and the proximal vein-to-artery junction (Fig. 5.3.4). However, a region of high WSS and low OSI is observed along the mid-cuff region, which appears to be the primary route for flow delivery. Changes in mean WSS magnitude and direction are most pronounced along the vein-to-artery junction, particularly at the toe and heel. Elevated contours of the WSSG and WSSAG also encompass the sinus region and extend to the arterial floor. In comparison to a similar un-cuffed conventional anastomotic configuration (Graft 2; Fig. 4.3.5), a moderate reduction in WSSG and WSSAG along the anastomotic suture-lines is realized with the Miller cuff.

For all virtually prototyped configurations, proximal outflow and the related separation along the upper graft surface result in low WSS and high OSI conditions at this location (Figs. 5.3.5-5.3.7). Surprisingly, highest OSI occurrence is observed for Model C, where velocity vectors indicate the least amount of separation due to inlet graft curvature (Fig. 5.3.7). WSSG and WSSAG contours are generally consistent among Models A – C, with significant occurrences very near the heel and elevated values continuing around the artery in a narrow band. In comparison to the Miller cuff and conventional models, graft and arterial curvatures which characterize Models A – C result in relatively low variations in WSS magnitude and direction, particularly at the toe. Minor variations in WSSG and WSSAG values are observed among the various inlet graft curvatures selected.

5.3.3 NWRT-Based Models

Convergent profiles of the NWRT parameter, based on 400,000 platelet trajectories, indicate significant particle-wall interactions along the vein cuff and sinus regions of the Miller configuration (Fig. 5.3.9a). The composite NWRT model, which includes conditions for platelet activation and surface reactivity (cf. Sect. 3.3), emphasizes particle-wall interactions most significantly along the graft to vein suture-line, and in the region of the heel (Fig. 5.3.9b). Consistent with the 4 mm artery and applied inlet conditions, a value of τ_{mean} = 14 dyne/cm^2 was used to compute PSH and SR factors. Surprisingly, little particle wall interaction is observed in the region of the arterial toe.

Regions of elevated particle-wall interactions along the grafts of Models A – C are consistent with the inlet curvatures and resulting secondary velocities (Fig. 5.3.9). Most significant particle-wall interactions are observed along the lower-half of the concave-up configurations (Models A and B), and along the upper-half of the concave-down design (Model C). Secondary vortical motions, as indicated in Fig. 5.3.2, result in significant particle-wall interactions along the lateral arterial walls, which span the length of the anastomoses (Fig. 5.3.9). In the region of the anastomotic toe, high flow conditions as well as a decrease in vortex strength associated with the curved arterial configuration begin to reduce significant NWRT values along the lateral surface. The inclusion of the platelet stimulation history (PSH) and surface reactivity (SR) factors increases composite NWRT contours along the suture-line of Models A – C, particularly at the heel (Figs. 5.3.9d, f, & h). However, significant arterial WSS-values throughout the anastomotic region moderately reduce composite NWRT contours through the inclusion of the SR factor. For the case of proximal outflow, it appears that the high-angle configuration (Model A) results in the least significant extent of composite NWRT occurrence. However, elevated contours of the NWRT parameter are observed near critical regions, such as the toe and suture-line, in all virtually prototyped models.

Considering the composite NWRT model for monocytes with a WSS-limiter condition (τ_{limit} = 14.0 dyne/cm^2), significant contours are observed at the heel and in the sinus region of the Miller cuff (Fig. 5.3.10a). As observed in Fig. (5.3.2), the concave-up graft-inlet configurations of Models A and B move the core of highest velocity flow toward the graft heel resulting in significant helical flow patterns in the anastomotic region. These significant secondary vortices effectively increase WSS values, particularly along the arterial lateral wall. Therefore, composite NWRT-values for monocytes are effectively limited in Models A and B. In contrast, the concave down graft configuration of Model C was observed to reduce secondary vortices in the region of the anastomosis, producing lower WSS values. Despite relatively less secondary transport in Model C, WSS conditions below τ_{limit} = 14.0 dyne/cm^2 result in significant composite NWRT values for monocytes throughout the junction region (Fig. 5.3.10d). Considering these results, a dual role for secondary vortical motion in DAIH formation is implicated. While secondary motion is often associated with the transport of critical blood particles to the vascular surface, particle-wall interactions may be mitigated by elevated WSS-values resulting from vortical flow patterns.

5.3.4 The Case of an Occluded Proximal Outlet

In the absence of proximal outflow, the low-angle virtually prototyped configurations (Models B and C) are expected to significantly mitigate disturbed flow and particle interactions with the vascular surface. However, the effects of inlet graft curvature warrant further analysis.

In the absence of proximal outflow, WSS values are significantly elevated distally and near zero in the proximal arterial segments of Models B and C (Figs. 5.3.11 and 5.3.12). In comparison to previous results including proximal outflow, separation and the resulting region of significantly low WSS along the upper graft surface have been largely eliminated. However, regions of low WSS are observed in proximal half of the virtually prototyped anastomoses, particularly near the heel (Fig. 5.3.11 & 5.3.12). Contours of the WSSG and WSSAG parameters are marginally reduced by the occluded proximal segment. However, significant WSSG and WSSAG values persist near the heel, which remains a site of flow separation.

Convergent NWRT profiles for platelets indicate significant particle-wall interactions along the lateral arterial surfaces of Models B and C (Fig. 5.3.13). However, NWRT contours are significantly reduced throughout the anastomotic region for the case of no proximal outflow (Figs. 5.3.13a & c vs. 5.3.9e & g). Significant helical vortices associated with Model B effectively decrease the surface reactivity and reduce the local time available for platelet activation. Furthermore, the concave-up configuration ensures that fast moving relatively unactivated particles are entrained in the anastomotic vortices. As a result, the composite NWRT values are not significantly altered by the inclusion of the PSH and SR factors. In contrast, the concave-down configuration of Model C shifts the core of highest velocity flow toward the upper graft surface producing lower velocities and WSS-values as well as allowing high residence time particles to enter the distal anastomotic region. The resulting composite NWRT-values are largely elevated for Model C throughout the anastomotic region. In comparison to the previous results, it appears that significantly lower NWRT contours are observed in the absence of proximal outflow. Moreover, the concave-up configuration of Model B reduces low WSS occurrence and mitigates the upstream residence time of vortically entrained platelets resulting in considerably lower composite NWRT-values.

5.4 Discussion

To assess the hemodynamic characteristics of anastomotic designs intended to improve graft performance, multiple pathways for DAIH formation have been considered. Previous studies suggesting improved anastomotic designs have focused on associations between DAIH formations and disturbed flow characteristics in the junction region (Lei et al., 1996 & 1997) including coherent vortices (Harris and How, 1999), regions of low WSS (Harris and How, 1999), and significant changes in WSS-vector direction and magnitude, as quantified by the WSSG, WSSAG, and OSI (Lei et al., 1996 & 1997; Longest and Kleinstreuer, 2000; Longest et al., 2000). However, a number of studies have established a significant biophysical role for critical blood particles, such as monocytes and platelets, in the initialization and progression of DAIH (Liu, 1999; Sottiurai et al., 1999). As described in

Sect. 3.6, interactions of activated platelets with a reactive vascular surface were found to qualitatively correlate with system specific observations of DAIH in canine models. Sites of significant particle-wall interaction were quantified by the composite NWRT model, which includes shear stress based factors for platelet activation as well as endothelial cell expression of thrombogenic and anti-thrombogenic compounds. Moreover, it has been established that regions of low WSS are an insufficient indicator of localized sites of significant particle-wall interactions. Persuasive *in vivo* evidence suggests that multiple endothelial responses to low WSS conditions are also capable of eliciting IH formations, in the absence of particle-wall interactions (Pearson, 1994; Sharefkin et al., 1991). Furthermore, an endothelial shape and/or signaling response capable of producing IH formations has been related to the gradients of the time-averaged WSS magnitude and direction (Helmke and Davies, 2002; Kleinstreuer et al., 2001; Nagel et al., 1999; Tardy et al., 1997; Vorp, 2002). Correlations were not identified between WSSG and WSSAG parameters and macroscopic observations of system specific sites of DAIH in Sect 3.6. However, it is proposed that signaling responses arising within focal regions of significantly elevated WSSG and WSSAG values dominate the regulatory nature of the endothelium resulting in spatially corresponding aggressive IH formations. For example, significantly elevated WSSG and WSSAG values along the suture-line of the anastomosis may be responsible for continued IH occurrence in this area beyond the reportedly short time required for healing of the surgical injury.

Considering the multiple pathways capable of eliciting DAIH, the current analysis evaluates graft performance with respect to vortical flow features, WSS conditions including variations in vector magnitude and direction, and particle-wall interactions as encapsulated by the composite NWRT parameter for platelets and monocytes. Factors such as compliance mismatch, intramural stress and strain, and surgical injury have not been directly assessed.

5.4.1 Evaluation of the Miller Cuff

Considering the Miller cuff, *in vivo* evidence suggests that a potential mechanism for the improved patency associated with below-the-knee placement (Stonebridge et al., 1997) is due to a redistribution of DAIH away from the critical arterial region (Kissin et al., 2000;

Leuprecht et al., 2002; Tyrrell & Wolfe, 1997). However, significant DAIH formations are typically observed throughout the venous cuff and particularly at the graft-to-vein interface, where it is better accommodated by larger cross-sectional areas (Kissin et al., 2000; Leuprecht et al., 2002; Tyrrell & Wolfe, 1997). It has been suggested that hemodynamic factors are not largely responsible for the presumably advantageous shift of DAIH formation in the Miller configuration. For instance, Kissin et al. (2000) employed an animal model to show that considerably more DAIH formed in a cuff constructed of PTFE, in comparison to a vein cuff. The significant increase of IH within the synthetic cuff, despite similar geometric configurations, suggests that the inclusion of a natural, less thrombogenic buffer zone dissipates the biochemical hyperplasic response along the arterial suture-line. Leuprecht et al. (2002) found reduced intramural stress and lower DAIH occurrence along the suture-lines of the Miller cuff, which are locations of reduced compliance mismatch compared to a conventional graft. However, Sottiurai (1999) suggests that compliance mismatch is not the cause of DAIH development, but it enhances the pathogenesis, whereas hemodynamic factors provide the underlying stimulus. In support of this view, current results indicate significantly reduced values of the WSSG and WSSAG in the region of the cuff-to-artery interface (Fig. 5.3.4), compared with a similar conventional design (Graft 2; Fig. 4.3.5). Furthermore, composite NWRT contours for platelets indicate a shift in elevated occurrence from the arterial suture-line of the conventional anastomosis (Graft 2; Fig. 4.3.8d) to the graft-to-cuff junction of the Miller configurations (Fig. 5.3.9b). These observations are largely consistent with the reported redistribution of DAIH away from the critical arterial region. Hence, hemodyamically induced conditions, including particle-wall interactions, may be partially responsible for the improved patency rates associated with Miller cuffs positioned below-the-knee. Nevertheless, the use of an autologous vein cuff most likely reduces the hyperplasic response in the region of the arterial suture-line. Furthermore, Stonebridge et al. (1997) observed an increased risk of technical errors associated with the conventional below-the-knee anastomosis compared with cuff construction, such that improved Miller cuff performance may not be due to the redistribution of DAIH.

5.4.2 Evaluation of Virtually Prototyped Designs

Based on a multiple-pathway view of DAIH formations, the current analysis has focused on unexpanded anastomotic designs intended to mitigate occlusive formations. It is expected that expanded anastomotic configurations, which successfully mitigate disturbed flow occurrence, will result in reduced WSS conditions as well as elevated particle residence times, potentially accelerating DAIH formations. In construction of the virtually prototyped models, anatomical features of several vascular junctions were considered. Interestingly, no structures within the arterial vasculature resemble the surgically implemented end-to-side distal anastomosis including proximal outflow. Arterial junctions that result in flow division include the aorta-celiac and carotid artery bifurcations. However, in contrast to the end-to-side floor region, these geometries include relatively focal flow dividers. While an anastomotic configuration closely resembling the carotid artery bifurcation would be most likely sound from a particle-hemodynamics point of view, clinical application including surgical construction appears difficult. In contrast to the arterial vasculature, the venous system is largely characterized by structures resembling the distal end-to-side anastomosis. Characteristics of these junctions have been implemented in the virtually prototyped models including a concave-up inlet configuration, a recipient vascular segment that is curved to minimize flow redirection (comparable to the curved artery segment of Models A – C), and an unexpanded anastomotic junction. However, venous junctions typically include proximal inflow. Furthermore, venous and arterial regions have been observed to respond differently to biophysical stimuli. Nevertheless, it is hypothesized that virtually prototyped anastomotic models consistent with anatomic bifurcations will provide the best possible minimization of DAIH occurrence resulting from hemodynamic and particle interaction factors.

Considering the unexpanded virtually prototyped designs (Models A – C), WSS-based hemodynamic wall parameters indicate reduced occurrences of the WSSG and WSSAG near regions critical to flow delivery. Furthermore, the unexpanded configurations result in elevated WSS conditions particularly in the distal anastomotic region. While the virtual prototypes appear generally consistent with respect to WSSG and WSSAG occurrence, the concave-up graft configurations (Models A & B) increase flow through a majority of the anastomotic junction region resulting in elevated WSS-values and secondary velocity motions. In contrast, the concave-down configuration (Model C) shifts the core of highest velocity flow toward the upper graft surface such that WSS-values and secondary velocities are reduced in the proximal anastomotic region. Secondary velocities, arising from flow division, are responsible for significant particle-wall interactions along the lateral wall in all configurations considered. However, NWRT contours indicate that increased secondary velocities in the arterial region reduce the time available for particle-wall interactions. Furthermore, elevated vortical flows in the arterial region reduce the time available for platelet activation and increase local WSS-values, which down-regulates surface reactivity. Therefore, it appears that while unavoidable secondary velocities result in significant transport toward the vascular surface, elevated velocities arising from the unexpanded and concave-up graft inlet configurations may potentially reduce particle wall interactions. Furthermore, the concave-up configurations appear superior due to the elevated anastomotic flow rates, increased WSS-values, and reduced NWRT occurrence.

Advantages of the curved arterial segment include elevated WSS, reduced WSS-based parameters, and mitigated particle-wall interactions in the immediate toe region. (Rotation of Models A – C indicates that significant NWRT values due not extend to the midplane in the region of the toe.) However, significant arterial curvature elevates particle-wall interactions along the lateral wall. As a consequence of the end-to-side configuration, arterial vortex rotation is in the upward direction near the lateral vascular surface. As the vortex advances, a downward slant of the arterial segment results in elevated particle-wall interactions along the lateral wall. However, reduced DAIH formation in the toe region is likely more significant with respect to graft function.

The elimination of proximal outflow resulted in reduced particle-wall interactions for the concave-up graft configuration only. Apparently, elevated velocities and WSS-values throughout the anastomosis are essential for the reduction of particle-wall interactions in the case of an occluded proximal segment. Nevertheless, significant NWRT contours persist along the immediate junction region and the lateral wall.

Compared to the pre-expanded configurations, the virtual prototypes considered result in significantly higher WSS-values and reduced particle-wall interactions, particularly near the critical toe region. For instance, the low-angle configuration of Graft 3 in the previous chapter (cf. Fig. 4.2.2) is characterized by a continuous and relatively smooth hood curvature. Nevertheless, significant particle-wall interactions were observed along the graft surface (Fig. 4.3.8f), and were consistent with the DAIH observations of Loth et al. (2002). The clinical performance of graft configurations depends largely on the ability of an anastomosis to accommodate some DAIH development, particularly in the region of the suture-line. As with the Miller cuff, larger anastomotic areas provide for moderate DAIH formations, possibly without threatening graft survival. Moreover, DAIH formations in expanded configurations may naturally optimize the anastomotic hemodynamics, resulting in a biophysical equilibrium prior to graft occlusion. However, the un-physiological flow features of the distal end-to-side anastomosis, including proximal outflow, make the occurrence of an equilibrium-scenario unlikely. Considering the unexpanded models, clinical testing is necessary to determine if DAIH formation, particularly along the suture-line and lateral wall, will significantly threaten graft survival.

Similar to the ‘persistent vortex’ observations of Noori et al. (1999), the current results indicate that increased secondary vortices are associated with elevated WSS-values and reduced NWRT occurrence along the lateral wall. However, anastomotic vortices are largely responsible for transporting critical blood particles to the vascular surface. Furthermore, the current results strongly indicate that the extent and localization of micro-scale particle-wall interactions, which result directly from convection and diffusion of discrete elements, cannot be appropriately assessed from velocity vector plots or particle trajectories images. Instead, a quantitative model, such as the effective NWRT approach, is necessary to approximate the likelihood of micro-scale particle-wall interactions including the effects of particle activation and surface reactivity. Consequently, anastomotic designs based on ‘persistent vortex formations’ and qualitative WSS assessments (Harris and How, 1999; Fisher et al., 2001a) may not perform as intended. For instance, Fisher et al. (2002) observed fifty Distaflo™ applications at various distal locations (popliteal and tibial) and reported a one-year cumulative patency rate of 39%. While comparable Miller cuff patency results are statistically similar (49%; Fisher et al., 2002), the failure rate of the Distaflo™ application appears unacceptably high.

5.4.3 Conclusions and Recommendations

While recent studies have suggested a variety of mechanisms potentially responsible for the improved clinical performance of the Miller cuff, current results indicate that hemodynamic conditions, including particle-wall interactions, may partially account for the redistribution of significant DAIH formations away from the critical arterial region. Nevertheless, the use of an autologous vein cuff is potentially the factor most responsible for the reduced hyperplasic response in the region of the arterial suture-line (Kissin et al., 2000). Furthermore, the suturing of a vein segment to the artery facilitates the surgical procedure, resulting in a higher likelihood of a technically sound anastomosis.

Considering the virtually prototyped models, anatomic features consistent with venous anastomoses reduced the particle-hemodynamic potential for DAIH formations in locations critical to flow delivery. For instance, a concave-up graft inlet configuration (Fig. 5.2.2) resulted in elevated particle velocities and WSS-values in the region of the anastomosis, which were observed to significantly reduce occurrences of the composite NWRT models for platelets and monocytes. Significant graft and arterial curvatures, as well as the application of an unexpanded design, reduced and redistributed WSS-based hemodynamic parameters and NWRT occurrence; however, the particle-hemodynamic potential for DAIH formation was not eliminated. Considering the proliferative nature of IH formations, it appears that eventual occlusion of the virtually prototyped configurations is expected.

In conclusion, the application of a multiple-pathway particle-hemodynamic model for IH in distal anastomotic designs indicates that occlusive formations are an inevitable consequence of the un-physiological distal end-to-side anastomosis, particularly for the case of proximal outflow. Nevertheless, surgical benefits of the end-to-side distal anastomosis, such as ease of construction and the ability to deliver proximal outflow, ensure its continued implementation until a better alternative is proven. As such, results of this study suggest the implementation of concave-up graft inlets, relatively unexpanded anastomotic configurations, and arterial curvatures which moderate flow redirection. Graft and arterial curvatures can be clinically accommodated by the use of prefabricated external supports. Relatively new graft fasteners, such as vascular staples and clips (Zegdi et al., 2001) may potentially reduce suture-line IH. Clinical testing will be necessary to determine if the unexpanded anastomotic design suggested can accommodate moderate IH formations, expected in the immediate junction and lateral wall regions, without significantly altering graft function.

Clinically viable alternatives to the distal end-to-side (ETS) anastomosis include end-to-end (ETE) junctions, which offer comparable patency rates for both above-the-knee and below-the-knee applications (Hoedt et al., 2001). However, ETS anastomoses are currently the preferred alternative in cases of occlusive peripheral disease due to ease of construction and the delivery of proximal outflow. For instance, ETS anastomoses facilitate the joining of standard 6 and 8 mm grafts to various sized arteries. Nevertheless, recent and potential innovations in vascular devices may increase the clinical viability of the ETE anastomosis, resulting in a physiologically sound structure that minimizes or eliminates DAIH formations.

A potentially viable ETE anastomotic configuration intended minimize DAIH occurrence and to facilitate non-invasive procedures is illustrated in Fig. 5.4.1a. Patient specific or custom manufactured grafts can potentially surmount the current ETE problem of unmatched prosthetic and vascular diameters. A gradual taper just proximal to the ETE anastomosis is likely most appropriate (Fig. 5.4.1a). Increased pre-surgical mapping of the vasculature as well as patient specific CFD predictions of post-surgical outcomes (cf. Ku et al., 2002) may provide the dimensions necessary for custom tapered configurations. As a cost effective alternative to patient specific manufacturing, diameter modifications, made by the surgeon or a surgical technician, to tailor commercially available grafts are recommended. The removal of a narrow-V from the graft-end and subsequent reconnection could result in any graft taper specified, cf. Fig. 5.4.1b. Closure of the excised portion of the graft via conventional suture techniques would likely be highly thrombogenic, such that an adhesion or fusion approach is recommended. Alternatively, a set of variably tapered mandrels (or forms) could be implemented in conjunction with even heating of standard PTFE to produce the necessary taper required to reduce diameter mismatch in the region of the anastomosis.

Recent and potentially revolutionary studies indicate that drug impregnated (or eluting) stents virtually eliminate DAIH formations. For instance, sirolimus- (or rapamycin-) eluting stents were found to result in virtually no IH formation within coronary vessels, particularly at the stent edges, after six months (Morice et al., 2002; Serruys et al., 2002).

Hence, the novel application of rapamycin-eluting stents to reduce or eliminate DAIH is suggested for the proposed ETE configuration (Fig. 5.4.1a). Due to the potential reduction of coagulation, vascular healing, and DAIH formation, the use of conventional ETE suture techniques is discouraged in this scenario. Instead, the tapered graft should be partially inserted in the arterial region. Deployment of an appropriately sized drug-eluting stent should result in a smooth anastomotic transition. The application of a non-constrictive collar similar to the tie-band connector of Chang et al. (2000) can then be implemented to secure the anastomosis via minimally intrusive teeth. Alternatively, recently developed vascular adhesives could be implemented to secure the anastomosis. The length of the drug-eluting stent should be sufficient to provide a non-thrombogenic buffer in the immediate region of the ETE anastomosis as well as in a portion of the proximally tapered synthetic graft, where the risk of thrombosis is increased.

While the suggested ETE design does not directly provide for flow to the proximal arterial vasculature, CT studies of distal ETS anastomoses suggest that rapid proximal occlusion is likely (Hoedt et al., 2001). Therefore, the advantage of ETS proximal outflow may be overstated. To accommodate conditions where proximal outflow is a necessity, implementation of multiple vascular conduits, each originating with a proximal ETS anastomosis and terminating with the suggested ETE distal configuration, is a possibility. Alternatively, branched synthetic conduits, similar to those implemented for aortoiliac replacement, are proposed. Indeed, this configuration would be most appropriate for bifurcating flows considering the presumed similarity to the physiologically sound carotid artery bifurcation. To minimize the occurrence of thrombosis associated with smaller conduits, main and branch diameters of 8 and 6 mm are suggested. As described above, multiple distal branch tapers could be readily implemented and hemodyamically sound ETE anastomoses could be constructed, via non-invasive techniques. Computational particle-hemodynamics simulations of this system will require further model development to address and incorporate issues such as intra-lumenal stress, particle-stent interactions, and the biochemical implications of rapamycin at the cellular level.